Overlapping phenotypes – a clinical and magnetic resonance imaging investigation of schizotypy and pervasive developmental disorders in adolescents with cognitive impairment

By

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DECLARATION

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10th May 2007

CONTRIBUTORS

This thesis has been composed using work undertaken as part of the Edinburgh Study of Comorbidity (ESC), hence a wide range of people have assisted with the data collection.

Professor E.C. Johnstone, Professor D.G.C. Owens, Dr P. Hoare, Dr W. Muir and Dr S. Lawrie conceived and designed the ESC; V. Moffat organised the recruitment of participants; Professor E.C. Johnstone and Professor D.G.C. Owens carried out the clinical assessments; Dr M. Spencer and Dr S. Gaur carried out many of the structured rating scales; J. Harris and R. Kuessenberg carried out the IQ assessments and R. Philip and Dr B. Moorhead assisted with the collection of the neuroimaging data. In addition, Dr A. McIntosh provided assistance with statistical issues, particularly with regard to the meta-analysis.

I contributed to the collection of the structured rating scales; devised the protocols for the manual delineation of brain regions-of-interest and implemented these with the assistance of R. Philip; implemented the automated methods of image analysis; performed the literature reviews; carried out the data analysis and wrote the manuscript.

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ABSTRACT

Introduction: The neurobiological bases of pervasive developmental disorders (PDD) and schizotypy are not well established. In addition there are clinical overlaps between the two which can make diagnostic determination difficult. The primary aim of this thesis was to explore the relationship between PDD and schizotypy by examining their associated clinical and brain structural features in a group of cognitively impaired adolescents. **Methods:** 138 adolescents receiving special educational assistance and 62 typically developing controls were recruited. Schizotypal features were measured using the Structured Interview for Schizotypy (SIS) and PDD features were measured using the Social Communication Questionnaire (SCQ). Each participant also received a standardised clinical interview and a magnetic resonance imaging (MRI) scan. Whole brain volume, midsagittal corpus callosum area and prefrontal lobe volume and gyrification index (GI) were measured using automated, semi-automated and manual region of interest techniques. The subjects in special education were considered in different groupings in three main analyses. In the first, the SIS was used to divide the subjects into those with and without schizotypal features. In the second, the standard SCQ cut-offs were used to divide the subjects into those with autism, those with non-specific pervasive developmental disorder (PDD-NOS) and those with neither. Finally, both the SIS and the SCQ were used contemporaneously to divide the subjects into 6 groups: schizotypal; autistic; PDD-NOS; comorbid schizotypy and autism; comorbid schizotypy and PDD-NOS; and neither schizotypal nor autistic. In each analysis the groups were compared to each other and to the controls with respect to the clinical features and brain structural measures. **Results:** The schizotypal subjects showed an increase in right prefrontal volume and changes in the anterior and posterior corpus callosum relative to those without schizotypy and the controls. The autism group had reduced right prefrontal GI relative to the other groups as well as anterior callosal

changes. The PDD-NOS group had the highest level of psychiatric symptomatology on the CIS, in particular those who were comorbid for PDD-NOS and schizotypy. This comorbid group, both clinically and structurally resembled the schizotypy group rather than the PDD-NOS group. **Conclusions:** Distinct neuroanatomical differences can be seen in educationally impaired adolescents with schizotypal features and in those with autistic features. These can be related to the observed clinical impairment and may help to distinguish these disorders in the future. It is possible that adolescents with features of both schizotypy and PDD-NOS suffer from an underlying schizophrenia spectrum disorder rather than an autistic spectrum disorder.

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Chapter 1

Historical Perspectives, Modern Diagnostic Criteria and Clinical Features Relevant to Schizotypy and Pervasive Developmental Disorders

1.1 The History of Schizotypy

Although there is no agreed definition of what the term schizotypy actually encompasses, it is used in modern day psychiatry to describe a combination of personality and behavioural features like those observable in the relatives of schizophrenic individuals (and possibly premorbidly in people with schizophrenia), and mild forms of the psychopathologies which are the key features of schizophrenia itself. It is not surprising therefore that the evolution of the term has been influenced by descriptions of the aberrant but non-psychotic relatives of individuals with schizophrenia, and by clinical observations of mild schizophrenia-like syndromes which do not meet diagnostic criteria for the full disorder.[1] The current usage of the term reflects a convergence of these family based and clinical approaches to describing the hinterlands of schizophrenia and has been strongly influenced by the Danish-American Adoption Study[2] and the subsequent operationalisation of diagnostic criteria for schizotypal personality disorder.

The conceptualisation of schizophrenia, not as a discrete entity, but rather as representing the severe end of a spectrum of disorder is not new and is in fact as old as the diagnosis of schizophrenia itself. In 1908 Eugen Bleuler, writing about schizophrenia noted:

> "If one observes the relatives of our patients…, one often finds in them peculiarities which are qualitatively identical with those of the patients themselves, so that the disease appears to be only a quantitative increase of the anomalies seen in the parents and siblings"[3]

Similar ideas were also held by Emil Kraeplin,[4] although it was Bleuler who proposed broadening Kraeplin's dementia praecox to include what he termed latent schizophrenia. He proposed latent schizophrenia as essentially a forme fruste of schizophrenia with

> "all the symptoms and all the combinations of symptoms which are present in the manifest type of the disease….irritable, odd, moody, withdrawn or exaggeratedly punctual people…often one discovers a concealed catatonic or paranoid symptom"[3]

He also suggested that it was the most common form of schizophrenia but that those affected rarely present for treatment.[3]

Other early investigators also noted unusual patterns of personality and behaviour in the relatives of schizophrenic patients. Kretschmer, who viewed the major psychoses as extreme ends of the continuum of normal, described schizoid personality not only in the relatives of schizophrenic patients but also as a premorbid personality trait in those who later went on to develop schizophrenia. According to Kretschmer the central features of the schizoid personality were solitariness, humourlessness and eccentricity.[5] He also described "autistic withdrawal" where the schizoid individual, being preoccupied with their own thoughts and interests, would shut themselves away from society. Kallmann, in a study of the pedigrees of over 1000 individuals with schizophrenia, found that schizophrenia occurred in approximately 10% of relatives of probands but schizoidia appeared in another 25%. He described two types of cases within schizoidia – borderline cases and schizoid psychopaths - both of which were characterised by deficits in social and emotional functioning with eccentricities and autistic preoccupations.[6]

The term schizotypy itself was first introduced in the 1950s by Rado in the form schizotype,[7] short for schizophrenic genotype. Rado, a psychodynamic psychotherapist, believed that the essential components of the schizotype were "an integrative pleasure deficiency" and a distorted awareness of the physical self. These core deficits led to

interpersonal dependency, oversensitivity to rejection, difficulty in forming relationships, fearfulness and cognitive disorganisation. He asserted that when under severe stress the schizotype was at high risk of developing full-blown schizophrenia. Meehl expanded on this idea further using the term schizotaxia to denote an inherited neurointegrative deficit which predisposed to schizophrenia, with schizotypy the behavioural phenotype of this deficit. To Meehl, schizotypy was comprised of four components – anhedonia, cognitive slippage (mild thought disorder), interpersonal aversiveness, and ambivalence. In a similar manner to Rado he posited that environmental influences acting on the schizotype determined whether or not they go on to develop schizophrenia.[8]

Certain themes run through much of the work described above in particular eccentricity, social withdrawal or autism, and anhedonia. Attenuated positive symptoms are included in Bleuler's latent schizophrenia but do not occupy a central position, while Rado's cognitive disorganisation (and hence Meehl's cognitive slippage) were initially regarded as secondary features. However, since its introduction by Rado the term schizotypy has been expanded to include mild positive symptoms which are not present in such a degree to permit the diagnosis of schizophrenia, including magical thinking and perceptual distortions. This largely results from the influence of the work of Hoch and colleagues in the late 1940s and 1950s who identified "schizophrenic-like" symptomatology in individuals who were in psychoanalysis for the treatment of neurotic disorders. Classified as having "pseudoneurotic forms of schizophrenia" these individuals were described as suffering from attenuated forms of schizophrenia with abnormal thought processes, tangentiality, perceptual distortions and brief psychotic symptoms.[9] Hoch's

work influenced the DSM-II criteria for the diagnosis of latent or borderline schizophrenia and most crucially those used in the Danish-American Adoption Study.[2]

Latent or borderline schizophrenia was included in DSM-II in 1968 as a diagnostic category to describe a disorder with many of the features of schizophrenia but without clear-cut psychotic symptoms. The Danish-American Adoption Study, which examined the biological relatives of schizophrenic adoptees, found borderline schizophrenia to be present in around 15% of relatives of schizophrenic adoptees compared to 1% of relatives of control adoptees.[2] The criteria used in this study to diagnose borderline schizophrenia were essentially the same as those proposed in DSM-II and comprised dysfunction in 5 domains: thinking (atypical and vague, ignores reality), experience (brief cognitive distortions, depersonalisation, micropsychosis), affective (anhedonia), interpersonal behaviour (lacks depth, chaotic), and psychopathology (multiple inconsistent neurotic symptoms and severe generalised anxiety).[2] This characterisation of borderline schizophrenia forms the basis of much of our current understanding of schizotypal personality disorder.

At this time the term schizoid remained in common use although, due largely to psychodynamic influences, had come to encompass a wide range of difficulties with intimacy and affection well beyond its original meaning. This was addressed with the advent of DSM-III, when the modern diagnostic categories relevant to schizophrenia spectrum disorders were developed.

1.2 Current Diagnostic Categories Related to Schizotypy

Schizotypal Personality Disorder

In preparation for the construction of DSM-III a re-examination of the Danish-American Adoption Study was carried out by Spitzer et al.[10] They reviewed 86 out of the 321 cases from the Danish-American Adoption Study, approximately half of which were diagnosed in the original study with borderline or possibly borderline schizophrenia with the remainder having non-schizotypy diagnoses. Based on these interviews Spitzer et al derived 8 criteria which they felt best discriminated these two groups and these were included in DSM-III under the label schizotypal personality disorder, which replaced borderline schizophrenia.[10] Kendler notes that schizotypal personality disorder contains some criteria which bear more resemblance to Bleuler's latent schizophrenia than DSM-II borderline schizophrenia and attributes this to an admixture of the two concepts in the minds of the original investigators in the Danish-American Adoption Study.[1] These 8 criteria were retained for DSM-IV with a ninth added to give the current definition of schizotypal personality disorder (Figure 1.1). Similar criteria were used in ICD-9 and in ICD-10 although interestingly in the latter the "personality" label has been dropped, thus schizotypal disorder is classified in the same section as schizophrenia and other non-affective, non-organic psychotic disorders.[11]

In figure 1.1 one can see that schizotypal personality disorder includes features identified by the early writers such as eccentricity and a lack of close relationships, as well as attenuated positive symptoms such as ideas of reference, magical thinking and unusual

perceptual experiences. This combination is a fairly close approximation of the modern usage of the term schizotypy although the attenuated positive symptoms are often regarded as more central to the diagnosis of schizotypal personality disorder (probably because they are often easier to elicit at clinical interview), an emphasis which is not inferred from the use of schizotypy. It is therefore worth mentioning the other Cluster A personality disorders, with which schizotypal personality disorder overlaps, and which include features of schizotypy, i.e. paranoid personality disorder and schizoid personality disorder.

A) A pervasive pattern of social and interpersonal deficits marked by acute discomfort with, and reduced capacity for, close relationships as well as by cognitive or perceptual distortions and eccentricities of behaviour, beginning by early adulthood and present in a variety of contexts, as indicated by five (or more) of the following:

1) ideas of reference (excluding delusions of reference)
2) odd beliefs or magical thinking that influences behaviour and is inconsistent with subcultural norms
3) unusual perceptual experiences, including bodily illusions
4) odd thinking and speech (eg. vague, circumstantial, metaphorical, overelaborate or stereotyped)
5) suspiciousness or paranoid ideation
6) inappropriate or constricted affect
7) behaviour or appearance that is odd, eccentric, or peculiar
8) lack of close friends or confidants other than first-degree relatives
9) excessive social anxiety that does not diminish with familiarity and tends to be associated with paranoid fears rather than negative judgements about self

B) Does not occur exclusively during the course of schizophrenia, a mood disorder with psychotic features, another psychotic disorder, or a pervasive developmental disorder and is not due to the direct physiological effects of a general medical condition

Figure 1.1
DSM-IV diagnostic criteria for schizotypal personality disorder

Paranoid and Schizoid Personality Disorders

Paranoid personality disorder shares a sense of suspicious mistrust with schizotypal personality disorder whereas schizoid personality disorder emphasises the significant detachment from social relationships and a restricted emotions (Figure 1.2 and 1.3 respectively). In DSM-II the term schizoid was used broadly and included some individuals with schizotypal features and some with other problems of intimacy and affection. With the development of DSM-III those with schizotypal personality disorder were separated off, the term avoidant personality disorder was introduced to describe those social difficulties with a more obviously neurotic basis and the diagnostic criteria for schizoid personality disorder were narrowed so that it became more closely reminiscent of its original meaning. The modern criteria for schizoid personality disorder closely resemble the autistic withdrawal and anhedonia central to the early descriptions of the relatives of schizophrenics and are given more prominence in the modern usage of schizotypy than they are in the clinical diagnostic criteria for schizotypal personality disorder. Thus the inclusion of the characteristics of schizoid personality disorder under the umbrella of schizotypy helps to emphasise the importance of these social and emotional features.

A) A pervasive mistrust and suspiciousness of others such that their motives are interpreted as malevolent, beginning in early adulthood and present in a variety of contexts, as indicated by four (or more) of the following

1) suspects, without sufficient basis, that others are exploiting, harming or deceiving him or her
2) is preoccupied with unjustified doubts about the loyalty of associates
3) is reluctant to confide in others because of unwarranted fear that the information will be used maliciously against him or her
4) reads hidden, demeaning or threatening meanings into benign remarks/events
5) persistently bears grudges, i.e. is unforgiving of insults, injuries or slights
6) perceives attacks on his or her character or reputation that are not apparent to others and is quick to react angrily or to counterattack
7) has recurrent suspicions, without justification, regarding fidelity of spouse or partner

B) Does not occur exclusively during the course of schizophrenia, a mood disorder with psychotic features, or another psychotic disorder and is not due to the direct physiological effects of a general medical condition

Figure 1.2

DSM-IV criteria for paranoid personality disorders

A) A pervasive pattern of detachment from social relationships and a restricted range of expression of emotions in interpersonal settings, beginning by early adulthood and present in a variety of contexts, as indicated by four (or more) of the following:

1) neither desires nor enjoys close relationships, including being part of a family
2) almost always chooses solitary activities
3) has little, if any, interest in having sexual experiences with another person
4) takes pleasure in few, if any, activities
5) lacks close friends or confidants other than first degree relatives
6) appears indifferent to the praise or criticism of others
7) emotional coldness, detachment or flattened affectivity

B) Does not occur exclusively during the course of schizophrenia, a mood disorder with psychotic features, another psychotic disorder, or a pervasive developmental disorder and is not due to the direct physiological effects of a general medical condition

Figure 1.3

DSM IV diagnostic criteria for schizoid personality disorder

1.3 Summary of Clinical Features of Schizotypy

A useful summary of the important characteristics of schizotypy is provided by those features examined in Kendler's Structured Interview for Schizotypy (particularly as this is the rating scale which is used later in this report). These are social isolation and introversion, oversensitivity, social anxiety, ideas of reference, suspiciousness, restricted emotion, magical thinking, illusions, psychotic-like symptoms, derealisation/depersonalisation, irritability and impulsivity as well as the clinical impression at interview of rapport, affect, organisation of speech/thought, odd/eccentric behaviour and suspiciousness. As we have seen these features are represented among the three cluster A personality disorders discussed above but are not fully captured by any single one of them.

1.4 History of Autism and Pervasive Developmental Disorders

The word autism is derived from the Greek "autos" meaning self and was first used by Bleuler in his description of schizophrenic individuals to describe an extreme narrowing of relationships and withdrawal into the self.[3] It continued to be used by early writers on schizophrenia and it was not until 1943 that it was first applied to describe the disorder that we now perceive as autism when Leo Kanner published his seminal case series of 11 children with what he described as "autistic disturbances of affective contact."[12] The characteristic features he described were a profound lack of affective contact with others; disturbances in communication (3 of the 11 children were mute); an insistent desire for sameness; a fascination with inanimate objects; high levels of certain skills such as memory, but major difficulties in other cognitive domains; and an attractive appearance. His clinical descriptions have stood the test of time and by and large are very similar to the modern day diagnostic criteria for autism, in particular the social difficulties, resistance to change of routine and language impairment (Figure 1.4). Less robust were the assertions he made over the following years implicating a lack of maternal affection as the cause of autism, although he would have been strongly influenced by the predominance of psychoanalytic theories at the time.

The following year, and apparently unaware of Kanner's report, Hans Asperger published his observations of 4 boys which he described as suffering from "autistic psychopathy."[13] In the main Asperger's patients presented with very similar clinical features to Kanner's but they did not display the same degree of language impairment. Asperger's paper,

written in German, was largely ignored until 1981 when it was "rediscovered" by Lorna Wing who proposed the diagnosis of Asperger syndrome to describe those children who possessed the characteristic social impairments of autism but who possessed normal language abilities.[14]

Kanner's description of autism was initially intended to be a narrow diagnostic concept describing a rare disorder. However, in the years following the publication of his original paper it was expanded to include many people with intellectual impairment or brain damage and isolated autistic symptoms. In addition, autism was felt to be part of childhood schizophrenia and the combination of these factors led to a rather wider concept of the disorder than Kanner intended.[15] Studies by Kolvin in the 1960s and 70s which distinguished autism from childhood schizophrenia in terms of age of onset, course, phenomenology and family history[16] helped to narrow the concept again. However in the 1980s it began to re-expand albeit in a different direction with Wing's description of Asperger syndrome.[14] This has led to current ideas of the autism spectrum where manifestations of autism can vary from mild to severe. Certainly the symptoms displayed in Asperger syndrome are such that it appears to be a mild form of autism (Figure 1.5) and family studies appear to concur with this conceptualisation.[17,18]

1.5 Clinical Symptoms and Diagnostic Criteria of Pervasive Developmental Disorders

In both DSM-IV and ICD-10 autism and Asperger syndrome are classified together under the rubric of pervasive developmental disorders (PDD). The diagnostic criteria for each are shown in Figures 1.4 and 1.5. In addition there are a number of other PDDs, the places of which in relation to the autistic spectrum are unclear. Rett's Disorder has been reported only in females (males with the disorder are thought to die in utero) and is characterised by a period of normal development followed by the development of multiple specific deficits including motor skills, social engagement and language. Childhood Disintegrative Disorder is defined by a period of normal development which can be up to 10 years long, followed by a rapid regression of previously acquired social and language skills and loss of motor skills and bowel and bladder control. Finally the diagnosis of non-specific pervasive developmental disorder (PDD-NOS) can be given when there is significant impairment of social interactions or stereotyped behaviours are present but the diagnostic criteria for other PDDs are not met. An example of this is atypical autism which includes "presentations which do not meet the criteria for autism because of late age of onset, atypical symptomatology or subthreshold symptomatology."[19] Generally speaking, the autism spectrum is usually regarded as including autism and Asperger syndrome, with Rett's Disorder and Childhood Disintegrative Disorder excluded and the place of PDD-NOS uncertain.

A) A total of six (or more) items from 1, 2, and 3 with at least two from 1, and one each from 2 and 3:

1) qualitative impairment in social interaction, as manifested by at least two of the following:
    a) marked impairment in the use of multiple nonverbal behaviours, such as eye-to- eye gaze, facial expression, body postures, and gestures to regulate social interaction
    b) failure to develop peer relationships appropriate to developmental level
    c) a lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (e.g., by a lack of showing, bringing, or pointing out objects of interest)
    d) lack of social or emotional reciprocity

2) qualitative impairments in communication, as manifested by at least one of the following:
    a) delay in, or total lack of, the development of spoken language (not accompanied by an attempt to compensate through alternative modes of communication such as gesture or mime)
    b) in individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others
    c) stereotyped and repetitive use of language or idiosyncratic language
    d) lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level

3) restricted, repetitive, and stereotyped patterns of behaviour, interests, and activities as manifested by at least one of the following:
    a) encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus
    b) apparently inflexible adherence to specific, non-functional routines or rituals
    c) stereotyped and repetitive motor mannerisms (e.g., hand or finger flapping or twisting or complex whole-body movements)
    d) persistent preoccupation with parts of objects

B) Delays or abnormal functioning in at least one of the following areas, with onset prior to age 3 years: social interaction; language as used in social communication; or symbolic or imaginative play.

C) The disturbance is not better accounted for by Rett's disorder or childhood disintegrative disorder.

Figure 1.4

DSM-IV diagnostic criteria for autism

A) Qualitative impairment in social interaction, as manifested by at least two of the following:

1) marked impairment in the use of multiple nonverbal behaviours, such as eye-to-eye gaze, facial expression, body postures, and gestures to regulate social interaction
2) failure to develop peer relationships appropriate to developmental level
3) a lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (e.g., by a lack of showing, bringing, or pointing out objects of interest to other people)
4) lack of social or emotional reciprocity

B) Restricted, repetitive, and stereotyped patterns of behaviour, interests, and activities, as manifested by at least one of the following:

1) encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus
2) apparently inflexible adherence to specific, non-functional routines or rituals
3) stereotyped and repetitive motor mannerisms (e.g., hand or finger flapping or twisting, or complex whole-body movements)
4) persistent preoccupation with parts of objects

C) The disturbance causes clinically significant impairment in social, occupational, or other important areas of functioning.

D) There is no clinically significant general delay in language (e.g., single words used by age 2 years, communicative phrases used by age 3 years).

E) There is no clinically significant delay in cognitive development or in the development of age-appropriate self-help skills, adaptive behavior (other than in social interaction), and curiosity about the environment in childhood.

F) Criteria are not met for another specific pervasive developmental disorder or schizophrenia.

Figure 1.5

DSM IV criteria for Asperger disorder

1.6 Clinical and Neuropsychological Overlaps Between Pervasive Developmental Disorders and Schizotypy

As mentioned above, autism and schizophrenia have been regarded as separate disorders since the work of Kolvin on the early 1970s.[16] However there is no doubt that similarities between the disorders do exist particularly with respect to the negative symptoms of schizophrenia. In a study of 21 individuals with chronic, treatment resistant schizophrenia Sheitman et al found that autistic features as measured by the Autism Behaviour Checklist correlated with the degree of negative but not positive symptoms.[20] Examining the issue from the opposite direction Konstantareas et al found that 50% of autistic individuals met diagnostic criteria for schizophrenia, disorganised type with negative symptoms.[21] In a direct comparison of autism and schizophrenia the autistic subjects were found to have significantly less positive thought disorder than schizophrenic subjects but with no difference in measures of affective flattening.[22] These findings indicate that negative symptoms are shared between the disorders but that autistic individuals do not show the same degree of positive symptomatology as is found in schizophrenia. It is important to note the possibility that negative symptoms of schizophrenia and autistic features are different phenomena which are simply difficult to distinguish clinically, but it is equally possible that they represent the same underlying pathophysiogical process.

There is some evidence that similar neuropsychological deficits are seen in autism and schizophrenia. A reduction in the capacity to perform Theory of Mind tasks (the ability

to infer mental states in others), although not part of the diagnostic criteria is a well documented feature of autism and Asperger syndrome and is thought to be central to many of the social deficits seen in these disorders.[23] Theory of Mind deficits have also been reported in schizophrenia[24] and in the relatives of individuals with schizophrenia[25] suggesting that a similar process may underlie the social deficits observed in both schizophrenia and PDD. In addition, faulty theory of mind processing has been proposed as central to the genesis of delusional ideation in schizophrenia.[26] Executive function deficits have also been reported in both schizophrenia and PDD.[27,28] People with PDD have also been found to have a preference for local over global processing, i.e. they focus more on detail rather than surrounding contextual information (decreased central coherence).[29] Studies of local-global processing in schizophrenia are equivocal with some reporting a preference for global processing while others report the opposite.[30,31]

There are few neuropsychological studies which have directly compared autism and schizophrenia and certainly too few to draw firm conclusions from. In general they tend to show both similarities and differences between schizophrenia and autism with respect to neuropsychological testing. Individuals with autism have been found to perform less well at tasks of recognising basic facial emotions than people with schizophrenia or their first degree relatives[32] and in addition, discrimination of autism from schizophrenia on 2 of the 11 subtests of the Weschler Intelligence Scales has also been reported in the same population.[33] Schneider reported similarities between autism and schizophrenia in digit symbol substitution and differences in a receptive language task and performance on the Wisconsin Card Sorting Test.[34] Goldstein et al used cluster analysis of scores on a

variety of neuropsychological tests covering general intelligence and executive function to divide a population of schizophrenic individuals into 4 sub-groups and compared these with a group of individuals with high-functioning autism. They found that one of the sub-groups of schizophrenic individuals displayed a similar neuropsychological profile to people with high functioning autism whereas the others did not.[35] Unfortunately there are no studies which compare mentalising abilities or central coherence (local-global processing between autism and schizophrenia.

Turning to schizotypy, it is clear even from a quick inspection of the DSM-IV criteria that there are clinical overlaps between pervasive developmental disorders and schizoid/schizotypal personality disorders. Social withdrawal and a preference for solitary activities along with a lack of affective expression and diminished social reciprocity are all features which are common to both sets of disorders. Further overlaps become obvious when one considers the psychiatric symptoms known to occur in PDD but which do not form part of the diagnostic criteria. Neurotic symptoms are especially common but high rates of delusional ideas have also been reported in particular persecutory and grandiose delusions.[36] Thought disorder, similar to that seen in schizophrenia, has also been reported in a study of autistic adolescents and adults.[37] It is not surprising therefore that 23.4% and 31.9% of patients with an autism spectrum disorder have been found to meet criteria for schizotypal and schizoid personality disorder respectively (compared with 4.9% and 12.3% of people with attention deficit hyperactivity disorder).[38] Additionally, in a survey of consultant child and adolescent psychiatrists in London the three most common features in adolescents suspected of

having a diagnosis of schizotypal personality disorder were odd behaviour, a lack of close friends and inappropriate or constricted affect, all features which could easily be confused with PDD.[39]

This overlap of diagnostic categories was considered in great detail by Sula Wolff who over the course of 30 years described a group of 149 children who she labelled as suffering from "schizoid personality disorder of childhood." It should be noted that at the time this diagnostic label was given the term schizoid personality disorder was used differently to how it is today and would have encompassed both the modern day schizoid and schizotypal personality disorders - Wolff herself later commented that in modern criteria a diagnosis of "schizotypal personality disorder" or "cluster A personality disorder" of childhood would actually be more correct. These children were generally referred for "marked difficulty in social adjustment at school" and are described as being solitary and sensitive (about themselves, not others) with occasional paranoid ideas; lacking empathy; possessing rigid preoccupations with their own interests; using odd metaphorical language and having unusual fantasy lives. Following Wing's description of Asperger syndrome Wolff noted that many of her own case series shared features of and would likely have met diagnostic criteria for Asperger syndrome (although appears never to have formally tested this).[40] She later suggested that the correct diagnostic label for such children should be "schizoid/Asperger disorder."[41] In ICD-10 schizoid personality disorder of childhood is included under Asperger syndrome.[11] Notably however, of the 149 children Wolff studied with schizoid personality disorder of childhood 5% were found to have developed schizophrenia in adulthood compared to

0.7% of control children.[41] Additionally in a subset of 32 of the schizoid children diagnostic continuity was demonstrated with schizotypal personality disorder in adulthood in 24 subjects (75%). There are other case studies which have also reported individuals who attracted a diagnosis of PDD as children but later went on to develop schizophrenia[42,43] and Sporn et al report that 25% of the children they studied with childhood onset schizophrenia had an initial diagnosis of autism spectrum disorder.[44] In addition, a recent family study which examined the prevalence of psychiatric illness in first degree relatives of people with Asperger syndrome found a substantially higher rate of schizophrenia (15%) than is present in the general population.[45] It is interesting that this relationship is not seen in family history studies of people with autism.[46]

Findings from the above studies raise two possibilities. The first is that the autism spectrum and the schizophrenia spectrum show clinical and neuropsychological overlaps but are distinct unrelated disorders. In this model the conversion from childhood PDD to adulthood psychosis and the increased prevalence of schizophrenia in first degree relatives of individuals with Asperger syndrome may relate to the misdiagnosis of schizotypal features as autistic ones. It should also be considered within this model that childhood PDD may be a non-specific vulnerability factor for the development of a later, unrelated psychotic illness (e.g. through increasing childhood adversity) although this would not explain the increased prevalence of schizophrenia in first-degree relatives of people with Asperger syndrome. The second possibility is that pervasive developmental disorders and schizophrenia spectrum disorders are related, overlapping disorders which share not only clinical features but also have common aetiological and/or

pathophysiological mechanisms. It is hoped that by examing the brain structure which underlies PDD and schizotypy this thesis may begin to elucidate the nature of the relationship between them.

Chapter 2

Literature Review of Structural MRI Studies of Schizotypy

2.1 Introduction

Given the known clinical and familial relationships between schizotypy and schizophrenia it is not unreasonable to propose that the former will show similar aetiological and pathophysiological mechanisms to the latter. There must however be an underlying reason (or reasons) why individuals with schizotypy do not display the more severe phenotype of schizophrenia. The investigation of brain structural abnormalities in schizotypy may therefore lead to a greater understanding of why some individuals progress to schizophrenia while others do not. Despite this there is a paucity of neuroimaging research which concerns schizotypy relative to the number of studies whichi examine schizophrenia. In those studies which do exist a variety of approaches have been adopted and this review is structured to reflect this. The majority of researchers have chosen to study schizotypal personality disorder (SPD), hence these are considered first. A second approach has been to use psychometric rating scales to measure schizotypal features and correlate these features with brain structure. Finally there are studies which examine unaffected family members of schizophrenic individuals. These are included here where there is some measure of schizotypy or psychotic symptomatology on which the relatives score more highly than controls. Studies of ultra high risk individuals have not been included, despite the prominence of schizotypal features in such groups, due to the high rates of progression to schizophrenia within a year (about 30%)[47] suggesting that many of these individuals are prodromal for schizophrenia rather than schizotypal.

2.2 Methods

Literature search

Medline, EMBASE and PsychINFO were searched for all English language studies published between January 1984 and March 2006 that reported structural MRI data in people with autism and unaffected controls. The search terms were "magnetic resonance imaging" combined using the AND operator with "schizotypal", "schizotypy", "schizoid", "schizophrenia spectrum" or combinations of both "schizophrenia" and one of "sibling", "twin", "offspring" "child", "progeny", "relative", "family" or "high risk" and related terms. Both free-text and expanded medical subject headings were used. Subject headings were adapted to the specific subject headings of the biomedical databases used. The search strategy was supplemented by including a cited reference search and inspecting the reference lists of included articles.

Criteria for inclusion

All abstracts were independently assessed for inclusion by two people (including the author), and articles in full text were retrieved if appropriate. Full text articles were then inspected independently by the same individuals. Any disagreements at either stage were resolved by discussion.

Primary research studies were considered for inclusion if they were published as a peer-reviewed article in English and compared subjects with schizotypy and a group of healthy controls or examined continuous relationships of schizotypal features with brain

structure. As detailed above these were divided into three groups: studies of subjects with a schizophrenia spectrum personality disorder (schizoid, schizotypal or paranoid personality disorder); correlation studies of schizotypal features and brain structure and studies of subjects with a family history of schizophrenia and features of schizotypy although without a formal diagnosis. Studies which reported data on schizotypal individuals in combination with other groups were not included.

2.3 Results

1053 articles were identified through the database search of which 163 were reviewed in full text. Of these 31 articles were suitable for the review: 24 concerned a schizophrenia spectrum personality disorder, 3 were correlational analyses of schizotypal features and 4 concerned individuals with a family history of schizophrenia who displayed features of schizotypy. Of the excluded articles 111 did not concern schizotypy, 8 were review articles, 5 were not structural MRI studies, 5 were not written in English and 3 contained no quantitative data. The articles included in the review are shown in Table 2.1.

Schizotypal Personality Disorder

Whole Brain and Intracranial Volume

Three studies have reported on the total brain volume in SPD, none of which found any significant difference between SPD and controls.[48-50] Similarly three studies have examined total intracranial volume and again report no difference in results.[51-53]

Total Cerebral Hemispheres

Suzuki et al found no difference between the SPD group and normal controls although the SPD group did have larger grey matter than subjects with schizophrenia.[54] A trend towards a reduction in cortical grey matter in SPD versus controls was found by Dickey et al although this did not reach statistical significance.[51] Neither study found any significant changes in cerebral white matter.

Study (year)	Schizotypy measure	Schizotypal Subjects		Schizophrenia Subjects		Controls / Non-schizotypal subjects		Covariates	Main Findings
		N	Mean / median age	N	Mean / median age	N	Mean / median age		
*Buchsbaum (1997)[55]	DSM-IV SPD	12 (11:1)	45.8	11 (10:1)	42.9	23 (21:2)	45.2	tbv	Enlarged lateral ventricles in SCZ compared to SPD and controls No difference between SPD and controls although tended to lie intermediate between controls and SCZ in temporal horn but not anterior horn or body
*Byne (2001)[56]	DSM-IV SPD	12 (11:1)	42.7	12 (11:1)	43.7	12 (11:1)	42.2	tbv	No difference in total brain volume. Reduced pulvinar in schizotypal and schizophrenia group. No difference in mediodorsal nucleus
**Dickey (1999)[57]	DSM-IV SPD	16 (16:0)	39.9	N/A	N/A	14 (14:0)	38.2	icv	Reduction in left superior temporal gyrus and reversed asymmetry in parahippocampal gyrus in SPD No differences in amygdala or hippocampus
**Dickey (2000)[51]	DSM-IV SPD	16 (16:0)	39.9	N/A	N/A	14 (14:0)	38.2	icv	Larger CSF in SPD but not due to larger ventricles
**Dickey (2002)[58]	DSM-IV SPD	21 (21:0)	38.0	N/A	N/A	22 (22:0)	38.4	icv	Smaller left Heschl's gyrus in SPD No difference in right Heschl's gyrus or bilateral planum temporale
**Dickey (2003a)[48]	DSM-IV SPD	21 (21:0)	37.1	N/A	N/A	19 (19:0)	38.4	icv	No difference in fusiform gyrus
Dickey (2003b)[59]	DSM-IV SPD	21 (0:21)	28.4	N/A	N/A	29 (0:29)	30.4	icv	No difference in superior temporal gyrus
*Downhill (2000)[60]	DSM-IV SPD	13 (12:1)	43.3	27 (20:7)	38.3	31 (23:8)	41.2	tbv	Increased anterior corpus callosum in SPD.
*Downhill (2001)[61]	DSM-IV SPD	13 (12:1)	43.3	27 (20:7)	38.3	31 (23:8)	41.2	tbv	Equally reduced temporal lobe grey matter (both in superior temporal gyrus and in remainder of lobe) in SPD and schizophrenia relative to controls. No differences in temporal lobe white matter

*Hazlett (1999)[49]	DSM-IV SPD	13 (12:1)	43.3	27 (20:7)	38.3	32 (25:7)	41.8	tbv	No significant differences in thalamus or whole brain volume
*Haznedar (2004)[62]	DSM-IV SPD	13 (12:1)	43.3	27 (20:7)	38.3	32 (25:7)	41.8	tbv	No significant differences in cingulate gyrus
†Job (2005)[63]	Relatives with transient or partial psychotic symptoms on PSE compared to relatives without	18 (-)	-	N/A	N/A	47 (27:20)	23.2	-	Reduction over time in left temporal lobe grey matter greater in symptomatic relatives than non-symptomatic ones
††Kawasaki (2004)[64]	DSM-IV SPD	25 (14:11)	25.0	25 (14:11)	25.8	50 (28:22)	24.0	-	VBM study. Frontotemporal reductions in schizophrenia and SPD although less widespread in SPD particularly in frontal regions
Keshavan (2002)[65]	Offspring with high scores on magical ideation-perceptual aberration scales compared to normal controls	17 (8:9)	15.6	N/A	N/A	22 (11:11)	14.6	icv	Smaller left amygdalo-hippocampal complex in offspring of schizophrenics compared to normal controls. No difference in right amygdalo-hippocampal complex or dorsolateral prefrontal cortex
Koo (2006)[52]	DSM-IV SPD	32 (0:32)	30.0	N/A	N/A	29 (0:29)	32.0	icv	Reduced caudate bilaterally in SPD associated with increased positive and negative symptoms and deficits in executive function and memory
†Lawrie (2001)[66]	Relatives with transient or partial psychotic symptoms on PSE compared to relatives without	41 (19:22)	21.2	N/A	N/A	101 (54:47)	21.1	tbv	Reduced whole brain in symptomatic subjects. No differences in prefrontal and temporal lobes, basal ganglia, thalamus and ventricles.
†Lawrie (2002)[67]	Relatives with transient or partial psychotic symptoms on PSE compared to relatives without	19 (7:12)	23.0	N/A	N/A	47 (27:20)	23.2	-	Reduction over time in right temporal lobe greater in symptomatic relatives than non-symptomatic ones.
**Levitt (2002)[68]	DSM-IV SPD	15 (15:0)	38.5	N/A	N/A	14 (14:0)	38.0	icv	Reduced caudate bilaterally in SPD associated with increased perseverative errors in working memory tasks

**Levitt (2004)[69]	DSM-IV SPD	15 (15:0)	38.5	N/A	N/A	14 (14:0)	38.0	-	Study of shape differences Higher caudate head in SPD
‡Matsui (2000)[70]	MMPI	N/A	N/A	N/A	N/A	59 (29:30)	26.8	icv	Normal population correlation study. Negative correlation between frontal lobe volume and anhedonia, paranoia and schizophrenia subscales of MMPI
‡Matsui (2002)[71]	MMPI schizotypal subscales (high and low)	N/A	N/A	N/A	N/A	42 (22:20)	20.3	-	Normal population correlation study. Correlation between lack of self control and reduced grey matter in supplementary motor area
Raine (1992)[72]	STA, Venables schizotypy scale, Social Anhedonia scale	N/A	N/A	N/A	N/A	17 (8:9)	33.9	-	Normal population correlation study. High schizotypal scores correlate with reduced prefrontal volume
Raine (2002)[50]	DSM-IV SPD (10), PPD (4) and both (2)	16 (14:2)	30.9	N/A	N/A	27 (23:4)	32.1		Reduced prefrontal volume which was non-significant once antisocial personality disorder controlled for. No difference in whole brain volume
*Shihabuddin (2001)[73]	DSM-IIIR SPD	16 (15:1)	43.3	42 (30:12)	37.8	47 (35:12)	38.3	icv	No difference in caudate volume. Reduced putamen in SPD and larger putamen in schizophrenia relative to controls
††Suzuki (2004)[74]	DSM-IV SPD	24 (13:11)	24.9	N/A	N/A	47 (25:22)	25.1	age, icv	Decreased right anterior limb of internal capsule in SPD. No difference in caudate or lentiform volumes
††Suzuki (2005)[54]	ICD-10 SD, DSM IV-SPD	25 (15:10)	25.5	53 (32:21)	25.3	59 (35:24)	24.3	age, icv, gender	Equally reduced amygdala and hippocampus in both SPD and schizophrenia relative to controls. No differences in parahippocampal gyrus. Increased middle frontal gyrus and reduced right straight gyrus in SPD compared to controls. Increased right superior and inferior frontal gyrus and bilateral middle frontal gyrus in SPD relative to schizophrenia.
††Takahashi (2002)[75]	ICD-10 SD	24 (12:12)	22.7	40 (20:20)	26.2	48 (24:24)	24.2	age, icv, gender	No difference in anterior cingulate gyrus in SD, decreased in schizophrenia

††Takahashi (2004)[76]	ICD-10 SD	26 (14:12)	24.9	58 (31:27)	25.8	61 (30:31)	24.5	age, height, gender, icv	No difference in perigenual gyrus size. Lack of normal gender differences in SPD and schizophrenia
††Takahashi (2005)[77]	ICD-10 SD	37 (24:13)	25.8	62 (32:30)	25.8	69 (35:34)	24.0	age, icv, medication, gender	No difference in short or long insular cortices between SPD and controls. Reduced in schizophrenia.
††Takahashi (2006)[53]	DSM-IV SPD	39 (24:15)	23.9	65 (35:30)	25.7	72 (38:34)	25.8	age, icv, medication, gender	Equally reduced left planum temporale and superior temporal gyrus in SPD and schizophrenia relative to controls. Reduced Heschl's gyrus in schizophrenia but not SPD relative to controls. No differences in planum polare.
††Yoneyama (2003)[78]	ICD-10 SD, MMPI	14 (5:9)	24.5	N/A	N/A	28	23.4	-	VBM study. Reduced grey matter in bilateral insula and left entorhinal cortex

Table 2.1

Structural MRI studies of schizotypy included in the review

DSM-IV - Diagnostic and Statistical Manual; ICD-10 – International Classification of Diseases; MMPI – Minnesota Multiphasic Personality Inventory; SPD – schizotypal personality disorder, SD – schizotypal disorder, - - no data available, N/A – not applicable, icv – intracranial volume, tbv – total brain volume

*, **, †, ††, ‡, ‡‡ - overlapping populations

Frontal Lobe

In a group of individuals with a mixture of paranoid personality disorder and SPD Raine et al found reductions in prefrontal grey matter volume which was associated with poorer performance on frontal lobe tasks. This difference was abolished when antisocial traits were controlled for.[50] Suzuki et al found differences in regional prefrontal areas between individuals with SPD, schizophrenia and normal controls. Specifically the SPD group had larger volumes of the middle frontal gyrus bilaterally and smaller volumes of the right straight gyrus than the normal controls. In addition subjects with SPD had larger right superior, right inferior and bilateral middle frontal gyri than the schizophrenia group.[54]

Temporal Lobe Structures

The studies which examined the temporal lobe and its subregions are shown in Table 2.2. The findings are conflicting but on balance suggest that the temporal lobe is affected in schizotypal personality disorder. Three studies report reductions in the superior temporal gyrus,[53,57,61] while one found no difference.[59] The negative study concerned only females while the others concerned males or mixed groups suggesting that females with SPD may have different neuroanatomical features to males. Other findings were more equivocal with positive and negative findings reported in one study each for the amygdala, hippocampus, Heschl's gyrus and the planum polare.

Cingulate Gyrus

Takahashi et al report a lack of right greater than left asymmetry in the anterior cingulate gyrus of female patients with SPD compared to normal controls with similar findings being seen in schizophrenia. No differences in the overall size of the anterior cingulate gyrus were seen.[75] In a separate study of the perigenual cingulate gyrus the same authors report no difference between SPD patients and either normal controls or schizophrenics although a lack of difference between genders which was seen in the normal controls.[76] Haznedar et al found no difference between SPD and controls in any part of the cingulate gyrus.[62]

Thalamus

Hazlett et al found that there were no differences in the total thalamic volume between individuals with SPD, schizophrenia and normal controls.[49] In a subset of this group Byne et al found the size of the pulvinar was reduced in both schizophrenia and SPD relative to controls, whereas the mediodorsal nucleus did not differ between the groups.[56]

Basal Ganglia

Studies which examined the basal ganglia are somewhat equivocal with 2 studies from the same group reporting reductions in caudate volume (one in males and one in females)[52,68] while 2 others report no difference between individuals with SPD and controls.[73,74] Additionally Shihabuddin et al found a reduction in the volume of the putamen in SPD relative to controls[73] whereas Suzuki et al found no difference in the size of the lentiform nucleus.[74]

Study (year)	Schizotypal Subjects N	Schizotypal Subjects Mean / median age	Schizophrenia Subjects N	Schizophrenia Subjects Mean / median age	Controls N	Controls Mean / median age	Covariates	Main Findings
*Dickey (1999)[57]	16 (16:0)	38.2	N/A	N/A	14	39.9	icv	Reduction in left superior temporal gyrus and reversed asymmetry in parahippocampal gyrus in SPD No differences in amygdala or hippocampus
*Dickey (2002)[58]	21 (21:0)	38.0	N/A	N/A	22 (22:0)	38.4	icv	Smaller left Heschl's gyrus in SPD No difference in right Heschl's gyrus or bilateral planum temporale
*Dickey (2003a)[59]	21 (21:0)	37.1	N/A	N/A	19 (19:0)	38.4	icv	No difference in fusiform gyrus
*Dickey (2003b)[59]	21 (0:21)	28.4	N/A	N/A	29 (0:29)	30.4	icv	No difference in superior temporal gyrus
Downhill (2001)[61]	13 (12:1)	43.3	27 (20:7)	38.3	31 (23:8)	41.2	wbv	Equally reduced temporal lobe grey matter (both in superior temporal gyrus and in remainder of lobe) in SPD and schizophrenia relative to controls. No differences in temporal lobe white matter
**Suzuki (2005)[54]	25 (15:10)	25.5	53 (32:21)	25.3	59 (35:24)	24.3	age, icv, gender	Equally reduced amygdala and hippocampus in both SPD and schizophrenia relative to controls. No differences in parahippocampal gyrus
**Takahashi (2006)[53]	39 (24:15)	23.9	65 (35:30)	25.7	72 (38:34)	25.8	age, icv, medication, gender	Equally reduced left planum temporale and superior temporal gyrus in SPD and schizophrenia relative to controls. Reduced Heschl's gyrus in schizophrenia but not SPD relative to controls. No differences in planum polare.

Table 2.2

Studies of temporal lobe structures in SPD

Abbreviations as in Table 2.1.

Corpus Callosum

Only one study examined the corpus callosum in SPD and reported enlargements of the anterior corpus callosum relative to normal controls. This is in contrast to patients with schizophrenia who were found to have reductions in the same region. The posterior callosum was found to be significantly reduced in schizophrenia and non-significantly reduced in SPD compared to controls.[60]

Lateral ventricles

Two studies examined the lateral ventricles in SPD.[51,55] Buchsbaum et al compared lateral ventricle volumes between individuals with schizotypal personality disorder, schizophrenia and normal controls. They found significant increases in the body of the lateral ventricle in schizophrenia compared to the subjects with SPD and normal controls. No significant differences were found between the SPD subjects and the controls, although for the temporal horn the SPD group tended to lie between the schizophrenia group and the controls.[55] In contrast Dickey et al found that the CSF volume was larger in SPD than in controls but that this was not attributable to ventricular volume.[51]

Other intracerebral areas

Suzuki et al report a reduction in the volume of the right anterior limb of the internal capsule in SPD compared to normal controls.[74] The same group also report reductions in the anterior and posterior insular cortices in schizophrenia compared to SPD and normal controls who did not differ in size.[77]

VBM Studies of Schizotypal Personality Disorder

There have been only two VBM studies of SPD, both from the same group. In an attempt to delineate a homogenous group of schizotypal individuals Yoneyama examined a group of patients who not only met diagnostic criteria for SPD but also scored highly on schizophrenia related code types on the Minnesota Multiphasic Personality Inventory (MMPI). They found decreased grey matter in the insular regions bilaterally and in the left entorhinal cortex compared to controls.[78] Kawasaki et al used VBM to look for differences between patients with SPD, those with schizophrenia and normal controls. The schizophrenia patients showed widespread frontotemporal reductions in grey matter compared to controls. The SPD group shared reductions in grey matter with the schizophrenia group in the left inferior frontal gyrus, insula, superior temporal and medial temporal gyri, although were less severely affected overall, particularly in the frontal lobe.

Studies utilising schizotypy rating scales

Raine et al examined the relationship between schizotypy and prefrontal lobe size in a group of 17 people using three rating scales - STA, Schizophrenism and Social Anhedonia. The first two measure positive symptoms of schizotypy while the third measures negative features. Higher levels of schizotypy were found to correlate significantly with reduced prefrontal lobe size, however major limitations of this study are the low field strength of the MRI scanner (0.15 Tesla) and the use of a single coronal slice to estimate prefrontal lobe size.[72] Similarly Matsui et al found that reduced frontal lobe volume correlated with schizophrenia related subscales in a non-clinical

population.[70] In a separate population the same group used VBM to look for grey matter correlations with scores on schizophrenia related subscales of the MMPI and found that lack of self control was related to reduced grey matter density in the supplementary motor cortex.[71]

Studies examining relatives of individuals with schizophrenia which have included an indication of schizotypal features

While there are many studies of relatives of individuals with schizophrenia only four gave any clear indication of the presence of schizotypal features. Three of these are from the EHRS where the features in question were the presence of transient or isolated psychotic symptoms, and one is from the Pittsburgh high risk study in which the relatives score more highly on scales of magical ideation and perceptual aberration. In the EHRS symptomatic subjects had significantly smaller brains than subjects without symptoms although there was a trend towards enlargement of the right prefrontal lobe and temporal lobes relative to the whole brain volume.[66] Using region of interest methods symptomatic subjects showed significantly greater reductions in right temporal lobe volumes over time than those without symptoms in addition to non-significant right prefrontal reductions.[67] Different changes over time were found in the same group using VBM, in that left temporal reductions occurred over time (as opposed to right).[63] The Pittsburgh study found that the schizotypal offspring had a smaller left amygdala-hippocampal complex compared to healthy controls after covarying for brain volume.[65]

2.4 Discussion

Methodological Issues

There is a general lack of research in this area compared to that on schizophrenia thus there is little replication of results and conclusions have to be drawn on limited data. In addition the majority of research concerns individuals with schizotypal personality disorder thus may not be representative of the entire spectrum of schizotypy. Although many studies examined relatives of people with schizophrenia few of these gave any information regarding schizotypal features which may be a missed opportunity. The studies which were included used reliable diagnostic methods and groups were generally well matched for age and gender. Possible confounders which were not often considered included IQ differences between subjects and controls, the presence of other psychiatric disorder in subjects and whether or not the schizotypal individuals had a family history of schizophrenia.

Main Findings

Despite the lack of available research it is possible to say that, in general, individuals with SPD share some but not all of the structural abnormalities which are present in schizophrenia. The shared abnormalities mainly lie in the temporal lobe whereas the prefrontal region may be relatively spared compared to schizophrenia and even show sub-regional enlargements relative to normal controls. These findings have led to the suggestion that in SPD individuals the prefrontal lobe acts to buffer anatomical abnormalities of the temporal lobe thus providing protection from the development of

schizophrenia.[79] This hypothesis must be balanced against the fact that in neuropsychological studies of schizotypy deficits in executive function are commonly seen.[50] It is possible that the non-uniformity of the prefrontal lobe structural changes reported by Suzuki et al[54] may account for this with some regions of the prefrontal lobe being relatively spared while others are not and functional imaging studies provide some evidence that this is indeed the case. In a functional MRI (fMRI) study using a visuo-spatial memory task Koenigsberg et al report decreased activation of the left prefrontal cortex with increased activation in the right middle frontal gyrus and prestriate cortex in schizotypal subjects relative to either normal controls or schizophrenic subjects,[80] a result which is consistent with the structural MRI findings of Suzuki et al.[54] Increased middle frontal gyrus activation during the Wisconsin Card Sorting Test (WCST - a widely used test of executive function) has also been reported using positron emission tomography (PET) in schizotypal individuals relative to normal controls. This increase in activation corresponded with better performance on the WCST while increased inferior frontal gyrus activation correlated with worse performance.[81] In a further PET study Buchsbaum et al report increased metabolic rates in Brodmann area 10 (BA10) in schizotypal individuals relative to normal controls.[82] Interestingly in the EHRS, increased right prefrontal cortical folding was found to distinguish individuals who went on to develop schizophrenia from those who did not. Increased right prefrontal volume was also reported in the same paper and it was the anterior middle frontal gyrus region in BA10 which showed the greatest amount of sulcal branching on post hoc review of the scans.[83] The one existing diffusion tensor imaging study in schizotypal personality disorder is also supportive of the theory of non-uniform deficits in the prefrontal lobe, finding a reduction

in fronto-temporal connectivity via the uncinate fasiculus but preserved fronto-limbic connectivity via the cingulum bundle.[84]

It is interesting to note that those studies which have examined normal populations have tended to show that increasing levels of schizotypy are associated with reduced prefrontal volume and have no relation with temporal lobe size. This stands in contrast to the results for SPD and raises the possibility that different underlying pathophysiological mechanisms may be at work. However there are only three such studies and interpretation is difficult as it is not clear whether any of the participants met criteria for SPD or whether they concerned only individuals with sub-diagnostic levels of schizotypal features.

Conclusions

It appears from the available literature that SPD is associated with temporal lobe structural abnormalities in a similar but less severe pattern as is seen in schizophrenia. These may in part be compensated for by a relatively intact frontal lobe thus preventing deterioration into schizophrenia. It is possible that different pathophysiological mechanisms account for the presence of schizotypal features in the general population than in people with SPD. These findings must be regarded as preliminary due to the lack of replication and future research needs to address this.

Chapter 3

Systematic Review and Meta-analysis of Structural MRI Studies in Pervasive Developmental Disorder

3.1 Introduction

While early writers proposed that autism was caused by a lack of maternal responsiveness[85] it is now widely accepted as neurodevelopmental in origin. However, until relatively recently little was known about the brain structure associated with the disorder. Increasingly sophisticated neuroimaging techniques have played a major role in the advancement of knowledge in this area, in particular the advent of magnetic resonance imaging (MRI) which has enabled researchers to examine the autistic brain in vivo in unprecedented degrees of detail. Over the past 20 years there have been many MRI studies of the brain in autism and a wide variety of regions have been identified as structurally abnormal. Unfortunately there is often disagreement between studies and the literature can appear contradictory.

For example, hypoplasia of cerebellar vermal lobules VI-VII was one of the first structural abnormalities found to be associated with autism[86] but while this finding has been replicated by some studies[87] others have failed to find such an association.[88,89] Vermal hypoplasia has also been identified in other neurodevelopmental syndromes[90] leading some authors to suggest that it is a non-specific effect of IQ rather than related to autistic features per se.[91] More recently interest has focused on the total brain volume in autism with some studies showing an enlargement [92] while others find no difference[93] in size. Several studies have reported that these differences are dependent on age with younger autistic subjects showing an enlargement that is not seen in their older counterparts.[94,95] However the exact age at which this distinction can be seen varies

between studies and brain enlargement has been reported in adult autistic populations.[96] Results for other brain regions also show inconsistencies. For example the amygdala has been variously reported to be enlarged,[92] reduced[97] or no different in size[98] relative to controls and a similar spread of results has been seen for the hippocampus.[92,98,99] One study found age dependent differences for the amygdala in a similar pattern to those reported for total brain volume although such a relationship was not seen for the hippocampus.[100]

Several reviewers have sought to draw together this literature qualitatively[101, 102] however the structural MRI literature in autism appears to hold few robust and consistently replicated findings. This impression may however reflect the fact that most studies of autism are small and underpowered. Meta-analytic techniques allow the combination of small studies together, effectively increasing power and hence the reliability of the result. The use of these techniques, in combination with qualitative review, may be of use in determining the neuroanatomy of autism spectrum disorders.

What follows is a systematic review of MRI studies of the brain in autism spectrum disorders with the methodology of meta-analysis applied to those brain regions for which sufficient numbers of publications were available. An analysis of the confounding effects of age, gender and IQ is included using meta-regression.

3.2 Methods

Literature search

Medline, EMBASE and PsychINFO were searched for all English language studies published between January 1984 and March 2006 that reported structural MRI data in people with autism and unaffected controls. Search terms included 'autism', 'Asperger syndrome', 'pervasive developmental disorder' and related terms combined using the AND operator with 'magnetic resonance imaging.' Both free-text and expanded medical subject headings were used. Subject headings were adapted to the specific subject headings of the biomedical databases used. The search strategy was supplemented by including a cited reference search and inspecting the reference lists of included articles.

Criteria for inclusion

All abstracts were independently assessed for inclusion by two people (including the author), and articles in full text were retrieved where appropriate. Full text articles were then inspected independently by the same individuals, according to study inclusion criteria. Any disagreements at either stage were resolved by discussion.

Primary research studies were considered for inclusion if they were published as a peer-reviewed article in English and compared a sample of autistic subjects with a group of healthy controls. These comprised studies where subjects were described as meeting recognised diagnostic criteria for autism or other pervasive developmental disorders, or were reported as having received such a diagnosis in the past. For the meta-analysis only

studies reporting structural MRI data where means and standard deviations were available (or could be extracted) for each group were included. If a study combined autism and other pervasive developmental disorders together it was not included in the meta-analysis.

Data abstraction

Structural data was extracted from all included studies and recorded onto a spreadsheet along with a description of the anatomical feature, the type and unit of measurement (area or volume) and characteristics of the subject and control groups which possibly confounded any observed difference (including age, gender ratio and IQ).

The majority of included studies provided full-scale IQ results from the Wechsler Adult Intelligence Scale (WAIS) or Wechsler Intelligence Scale for Children (WISC) as appropriate to the age of the subjects. When verbal and performance IQ results were provided separately these were processed into full-scale IQ results according to standard protocols (WAIS manual).

Data were utilised in the meta-analysis when volume or area results were available for a region of interest from three or more studies. Where both volume and area data were available, only volumes were considered. Area and volume data were never combined in the same analysis. Additionally, where a study reported raw and adjusted values, the unadjusted values were utilised. When there was evidence of repeat publication, only the study with the most data for each specific region of interest was chosen. When a study

gave means by age and IQ stratified subgroups these were combined to give a pooled mean and standard deviation. However, for the purposes of the meta-regression the values for each subgroup were also recorded separately.

Data synthesis

Statistical analyses were conducted using STATA SE version 8 (STATA Corp, College Station, TX). Hedge's unbiased estimator of standardised effect size,[103] and its variance, was calculated from each study using the pooled means and standard deviations such that each study contributed only one data point per region of interest to the meta-analysis. Standardised effects sizes were then combined using random-effects meta-analysis using techniques based on the method of maximum likelihood.[104] A random-effects approach was chosen over the more conventional fixed-effects analysis due to the likelihood that results may truly vary between studies, for example due to differences in population age and IQ, as opposed to differing through chance alone. A random-effetcs analysis is therefore more conservative. Publication bias was assessed using Egger's test. The size of between-study heterogeneity was estimated using the I^2 statistic (a measure of the proportion of variance in summary effect size due to heterogeneity) and its statistical significance calculated using Cohen's Q.[105] Where I^2 exceeded 50% and for the total brain volume, the modifying effects of age, gender and IQ were investigated using meta-regression. Only studies for which age, gender and IQ data were available were included in the meta-regression and when studies provided data in age or IQ defined subgroups these were considered as separate data points in the appropriate analysis. A regression model was fitted to the data with the mean age and IQ of autistic subjects fitted as fixed

effects.[103] Study was modelled as a random effect and the model estimated using residual maximum likelihood (REML). Where significant relationships were found their nature was investigated graphically by fitting the ordinary least squares line to the data points. The meta-regression was also repeated using the pooled mean values to ensure that the results were not related to one study contributing a disproportionate number of data points to the analysis.

Qualitative Reviews

Qualitative reviews were carried out for those studies which included subjects with pervasive developmental disorders other than autism, voxel-based morphometry studies and for regions-of-interest which were examined in fewer than 3 separate studies.

3.3 Results

The literature search of the three databases yielded 656 articles and a further 2 articles were identified through the supplementary search strategies. Figure 3.1 summarises the study flow and reasons for exclusion.

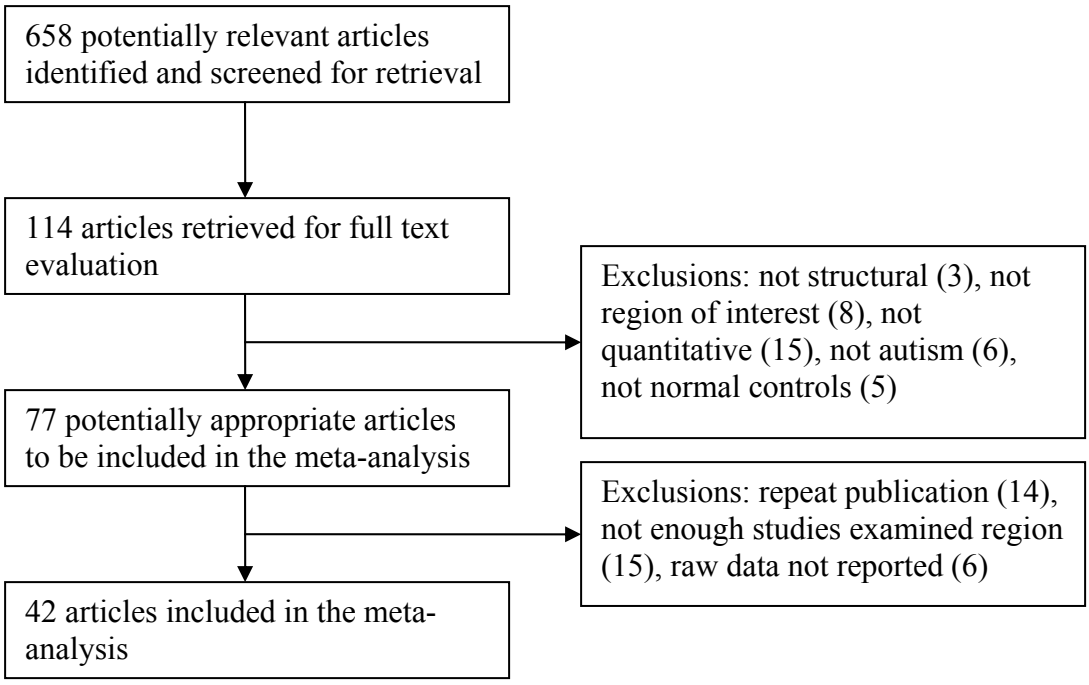

Figure 3.1
Study flow and reasons for exclusion from the meta-analysis

42 publications were included in the meta-analysis and provided information regarding 18 regions of interest from almost 800 individuals with autism and a similar number of controls. The exact number could not be calculated as overlapping groups of subjects provided data for different brain regions in different publications. Table 3.1 lists the demographic and diagnostic information for each study report included in the meta-analysis. Those with overlapping populations are indicated and results by age group are recorded in italics under the pooled means and standard deviations of the parent study.

		Autistic Subjects			Control Subjects			
Study (year)	**Diagnostic instruments**	**N (M:F)**	**Mean / median age**	**Mean IQ**	**N**	**Mean / median age**	**Mean IQ**	**Regions Used**
*Akshoomoff (2004)[106]	DSM-IV, CARS, ADI, ADOS	42 (42:0) *30* *12*	3·8 *3·8* *3·8*	67 *57* *86*	15 (15:0) *15* *15*	3·6 *3·6* *3·6*	111 *111* *111*	cbr, cbl, I-V, VI-VII
Aylward (2002)[95]	ADI, ADOS	67 (58:9) *23* *20* *24*	18·8 *10* *15* *32*	102·7 - - -	83 (76:7) *28* *27* *28*	18·9 *10* *15* *32*	107 - - -	tbv
Carper (2000)[107]	DSM-IV, CARS, ADI, ADOS	42 (42:0)	5·4	79·5	29 (29:0)	6	114	VI-VII
*Carper (2002)[108]	DSM-IV, CARS, ADI, ADOS	38 (38:0) *12* *19* *7*	5·7 *3·5* *5·7* *9·4*	- - - -	39 (39:0) *8* *17* *14*	6.5 *3·4* *5·7* *9·3*	- - - -	tbv
Cieseilski (1997)[109]	DSM-III-R	9 (5:4)	16·8	-	10 (7:3)	16·6	-	I-V, VI-VII, pons
Courchesne (1994)[110]	DSM-III	50 (41:9)	-	-	53 (43:10)	18·8	-	I-V, VI-VII
Egaas (1995)[111]	DSM-III-R, CARS, ADI, ADOS	51 (45:6)	15·5	-	51 (45:6)	15·5	-	cc
Elia (2000)[112]	DSM-IV, CARS	22 (22:0)	10·9	-	11 (11:0)	10·9	-	cc, mb, pons, vermis, VI-VII
†Gaffney (1987)[113]	DSM-III	13 (10:3)	11·3	84·9	35 (21:14)	12	-	cc
†Gaffney (1988)[114]	DSM-III	13 (10:3)	11·3	84·9	35 (21:14)	12	-	med, mb, pons
‡Garber (1989)[115]	DSM-III	15 (11:4)	11·6	-	15 (11:4)	-	-	4V
‡Garber (1992)[116]	DSM-III	12 (9:3)	27·2	-	12 (8:4)	26·4	-	4V, pons, vermis, I-V, VI-VII
**Hardan (2000)[117]	ADI, ADOS	22 (22:0)	22·4	100·4	22 (22:0)	22·4	100·5	Cc
**Hardan (2001)[118]	ADI, ADOS	16 (16:0)	22·2	102·8	19 (19:0)	22·2	101·2	icv, cbr
**Hardan (2001)[88]	ADI, ADOS	22 (22:0)	22·4	100·4	22 (22:0)	22·4	100·5	cbl, vermis, I-V, VI-VII, VIII-X, 4V, med, mb, pons
Hardan (2003)[119]	ADI, ADOS	40 (38:2)	19·3	103·1	41 (39:2)	18·6	104·2	tbv, caudate
Hardan (2004)[120]	ADI, ADOS	30 (30:0) *12* *18*	21·8 *12·7* *27·8*	101·8 *104·9* *99·7*	32 (32:0) *13* *19*	21·7 *12·8* *27·7*	105·3 *110·2* *102*	tbv

Hashimoto (1995)[87]	DSM-III-R, CLAC	102 (76:26) *11* *42* *10* *11* *3* *8* *8* *4* *5*	6·1 *1* *3* *5* *7* *9* *11* *13* *15* *18*	-	112 (65:47) *25* *20* *7* *12* *8* *15* *12* *9* *4*	7·2 *1* *3* *5* *7* *9* *11* *13* *15* *18*	-	vermis, I-V, VI-VII, VIII-X, 4V, med, mb, pons
††Hazlett (2006)[121]	DSM-III-R, ADI	23 (23:0)	19·1	89·9	15 (15:0)	21·6	102·3	Cbr
Haznedar (2000)[98]	DSM-IV, ADI	10 (-:-)	-	-	17 (15:2)	28·8	-	tbv, amy, hc
Herbert (2003)[122]	DSM-III-R, WADIC	17 (17:0)	-	>80	15 (15:0)	-	>80	tbv, caudate, cbl
Holttum (1992)[123]	DSM-III-R, ADI, ADOS	18 (18:0)	20·2	94·5	18 (18:0)	20·2	95·2	I-V, VI-VII, VIII-X
Howard (2000)[99]	DSM-IV	10 (10:0)	23·8	99	10 (10:0)	24·2	102	icv, cbr, amy, hc
Hsu (1991)[124]	-	34 (27:7)	18·9	82·6	44 (40:4)	19·8	113	mb, pons
Kates (2004)[125]	ABC, ADI-R, ADOS	8 (7:1)	7·6	69·6	16 (14:2)	8·3	123·6	Tbv
Kaufmann (2003)[90]	DSM-IV, ADI, ADOS	10 (10:0)	6·9	66·1	21 (21:0)	8·3	120·8	I-V, VI-VII, VIII-X
Kleiman (1992)[89]	DSM-III-R	10 (8:2)	6·6	-	17 (-:-)	-	-	pons, I-V, VI-VII
Levitt (1999)[126]	DSM-IV, ADI	8 (-:-)	12·5	83·3	21 (-:-)	12	114·9	VIII-X
Lotspeich (2004)[127]	ADI, ADOS	31 (31:0)	11·9	-	21 (21:0)	12·5	-	cbr
McAlonan (2005)[128]	ADI-R	17 (16:1)	12	101	17 (16:1)	11	114	tbv
Pierce (2001)[97]	DSM-IV, CARS, ADI, ADOS	6 (6:0)	29·5	83·7	8 (8:0)	28·3	-	amy
Piven (1992)[129]	DSM-III-R, ADI	15 (15:0)	27·7	92·5	30 (30:0)	29·6	115	pons, I-V, VI-VII
††Piven (1995)[96]	DSM-III-R, ADI	22 (22:0)	18·4	90·8	20 (20:0)	21·6	103·4	tbv

††Piven (1996)[130]	DSM-III-R, ADI	35 (26:9)	18	91	36 (20:16)	20·2	102·1	icv
††Piven (1998)[131]	DSM-III-R, ADI	35 (26:9)	18	91	36 (20:16)	20·2	102·1	hc
Rojas (2004)[132]	DSM-IV, ADI, ADOS	15 (13:2)	30·3	97·5	17 (8:9)	43·6	121·8	tbv, amy, hc
Schumann (2004)[100]	ADI-R, ADOS	39 (39:0) *19* *20*	12·9 *10* *15·5*	74·8 - -	22 (22:0) *11* *11*	13·1 *10* *15·5*	115 - -	cbr, amy, hc
††Sears (1999)[133]	DSM-III-R, ADI	35 (26:9)	18	91	36 (20:16)	20·2	102·1	caudate
Sparks (2002)[92]	DSM-IV, ADI, ADOS	29 (26:3)	3·9	-	26 (18:8)	4	-	tbv, cbr, cbl, hc, amy, caudate
Townsend (1999)[134]	DSM-III-R, CARS, ADI, ADOS	15 (-:-)	27	79	43 (-:-)	36·3	116	icv, tbv
Tsatsanis (2003)[135]	DSM-IV, ADI, ADOS	12 (12:0)	21	106·4	12 (12:0)	18·1	108·8	tbv
Vidal (2006)[136]	DSM-IV, ADI, ADOS	24 (24:0)	10	95·9	26 (26:0)	11	104·8	tbv, cc

Table 3.1

Demographic characteristics of included study populations

–: no data available, DSM: Diagnostic and Statistical Manual, III: third edition, IIIR: third edition revised, IV: fourth edition, ADI: Autism Diagnostic Inventory, ADOS: Autism Diagnostic Observational Schedule, CARS: Childhood Autism Rating Scale, WADIC: Wing Autistic Disorder Interview, CLAC: Checklist for the Autistic Child, icv: intracranial volume, tbv: total brain volume, cbr: cerebral hemispheres, cbl: cerebellum, amy: amygdala, hc: hippocampus, cc: corpus callosum, med: medulla, mb: midbrain, 4V: 4th ventricle

*, **, †, ††, ‡: studies with overlapping subject groups.

Age and IQ stratified results, when given, are entered under the pooled means for each study in italics

Meta-analysis and meta-regression

Standardised effect sizes (denoted by ES in the text), and their 95% confidence intervals, for the 18 regions of interest are presented in Table 3.2 along with estimates of heterogeneity. Statistically significant effects were obtained for 9 regions of interest. In order of effect size, areas of the midbrain (ES -0·77), vermal lobules VIII-X (ES -0·43), the corpus callosum (ES -0·28) and vermal lobules VI-VII (ES -0·27) were significantly smaller in autistic subjects compared to controls. In contrast, cerebellar (ES 0·72), cerebral hemisphere (ES 0·62) intracranial (ICV, ES 0·51), caudate (ES 0·41) and total brain (TBV, ES 0·33) volumes were significantly increased in autistic subjects compared to controls. Substantial overlaps in the confidence intervals indicated that there were no significant differences in the magnitude of the effect sizes between regions.

Statistically significant heterogeneity was seen for 9 of the 18 regions examined including several for which no differences between autistic subjects and controls were found. Significant relationships were found between the effect size for the cerebellar vermal lobules VI-VII and the mean age ($p=0·02$) and IQ ($p<0·01$) of the autistic subjects. Graphical representation of these relationships indicated that as subject age and IQ increase the observed reductions in vermal lobules VI-VII become less apparent (Figure 3.2 & 3.3). In addition significant relationships were found between age and effect size for the left and right amygdalae ($p=0·04$ and $p=0·01$ respectively). The graphs for both demonstrate that as age increases amygdala volume in autistic subjects decreases relative to controls (Figure 3.4). There were no significant relationships with age, gender or IQ for any of the other regions including for age and total brain volume ($p=0·22$)

(Figure 3.6). In line with a previous meta-analysis [137] a 2nd order regression line was fitted to the age-total brain volume data which was also non-significant. There were no significant changes to these relationships when the pooled mean values were used.

Anatomical Region	Number of studies‡	Standardised effect size (95% CI)	Heterogeneity I^2 (%)	Heterogeneity χ^2, p-value	Publication bias p-value
Volumes					
TBV	14 (19)	0·33 (0·14, 0·51)†	31·8	19·07, 0·12	0·51
ICV	4	0·51 (0·20, 0·81)†	0·0	1·23, 0·75	0·39
Cerebrum	7 (8)	0·62 (0·39, 0·86)†	0·0	5·36, 0·50	0·79
Cerebellum	4	0·72 (0·40, 1·03)†	0·0	0·88, 0·83	0·25
Caudate	3	0·41 (0·12, 0·71)†	0·0	1·58, 0·46	0·62
Amygdala L	6 (7)	0·15 (-0·46, 0·76)	75·8	20·68, <0·01	0·31
Amygdala R	6 (7)	0·28 (-0·32, 0·88)	74·9	19·94, <0·01	0·16
Hippocampus L	6	0·41 (-0·11, 0·93)	74·5	19·64, <0·01	0·78
Hippocampus R	6	0·29 (-0·27, 0·86)	78·8	23·56, <0·01	0·72
4V	3	0·22 (-0·28, 0·72)	28·4	2·79, 0·25	0·70
Areas					
I to V	9 (17)	0·10 (-0·28, 0·49)	71·5	42·97, <0·01	0·46
VI to VII	12 (20)	-0·27 (-0·51, -0·03)†	52·0	32·53, 0·03	0·38
VIII to X	5 (13)	-0·43 (-0·80, -0·06)†	49·5	18·78, 0·09	0·76
Total vermis	4 (12)	-0·22 (-0·51, 0·07)	20·7	13·83, 0·24	<0·01
Medulla	3 (11)	-0·99 (-2·17, 0·18)	92·8	34·73, <0·01	0·62
Midbrain	5 (13)	-0·77 (-1·52, -0·02)†	90·2	47·38, <0·01	0·52
Corpus callosum	5	-0·28 (-0·52, -0·03)†	0·0	0·43, 0·98	0·21
Pons	9 (17)	-0·53 (-1·19, 0·13)	90·6	97·31, <0·01	0·42

Table 3.2

Effect sizes and estimates of heterogeneity and publication bias for the 18 regions of interest

‡ Numbers in brackets represent the total number of data points used in the age meta-regression

† Significant at p<0·05

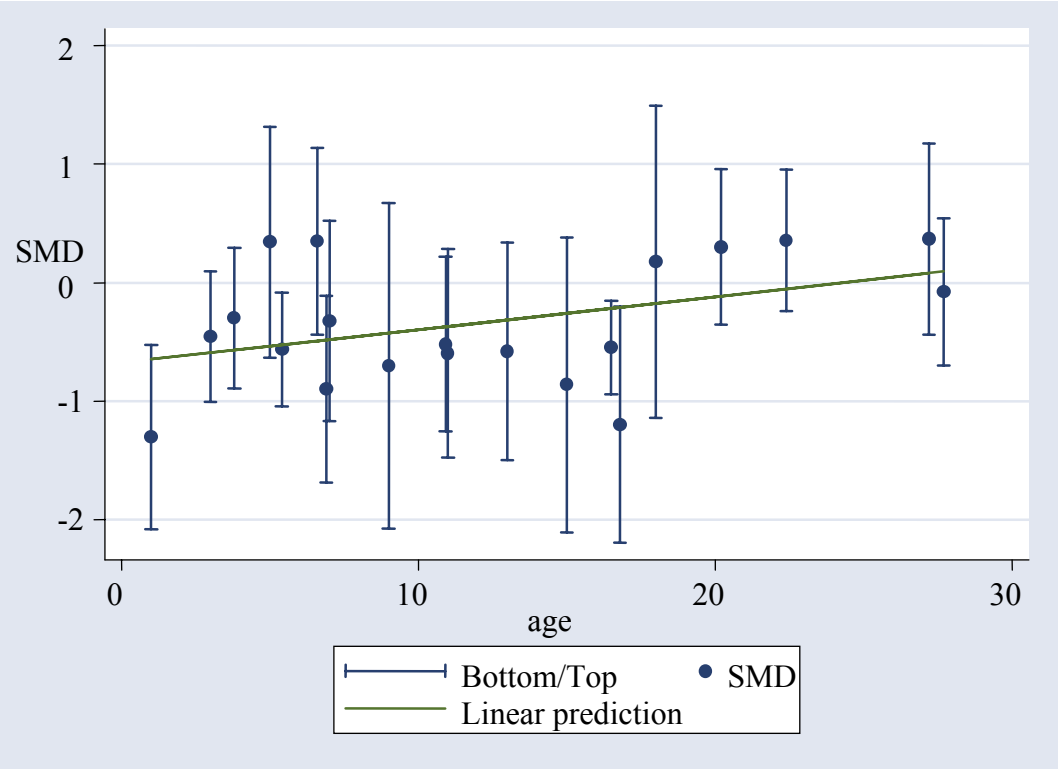

Figure 3.2

Graph of standardised mean difference (SMD) versus mean age of the autistic groups for vermal lobules VI-VII

When studies provided data in age stratified subgroups these are shown separately

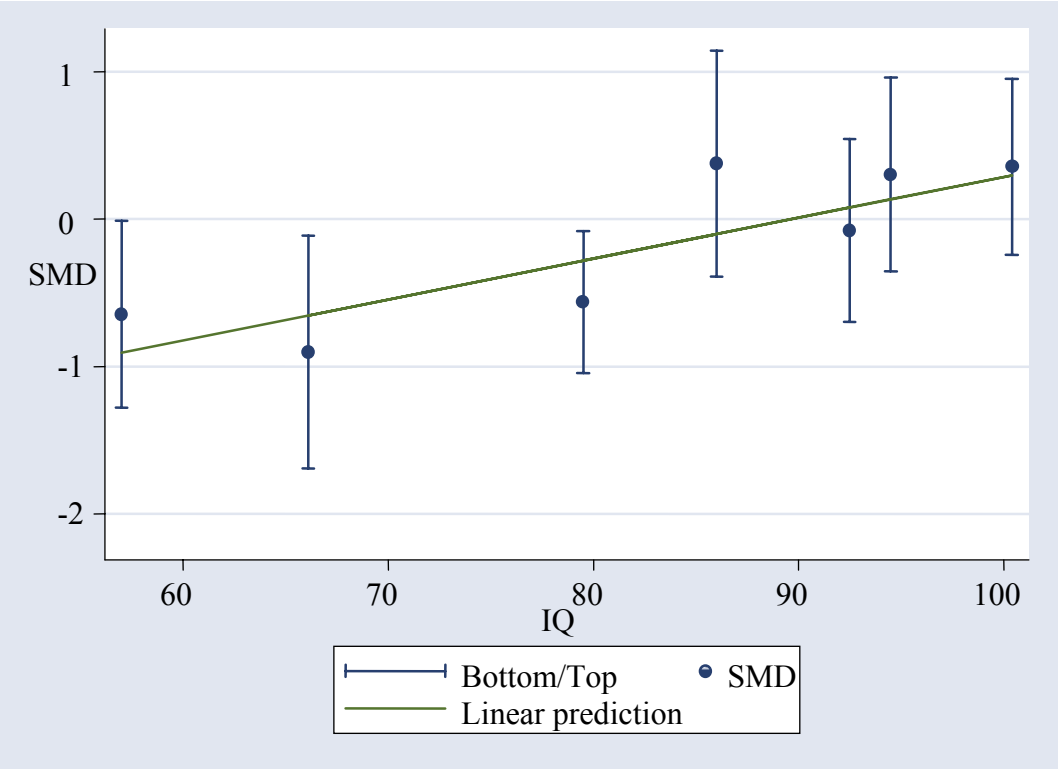

Figure 3.3

Graph of standardised mean difference (SMD) versus mean IQ of the autistic groups for vermal lobules VI-VII

Only studies reporting IQ results are included and when studies providing data by IQ stratified subgroups are shown separately

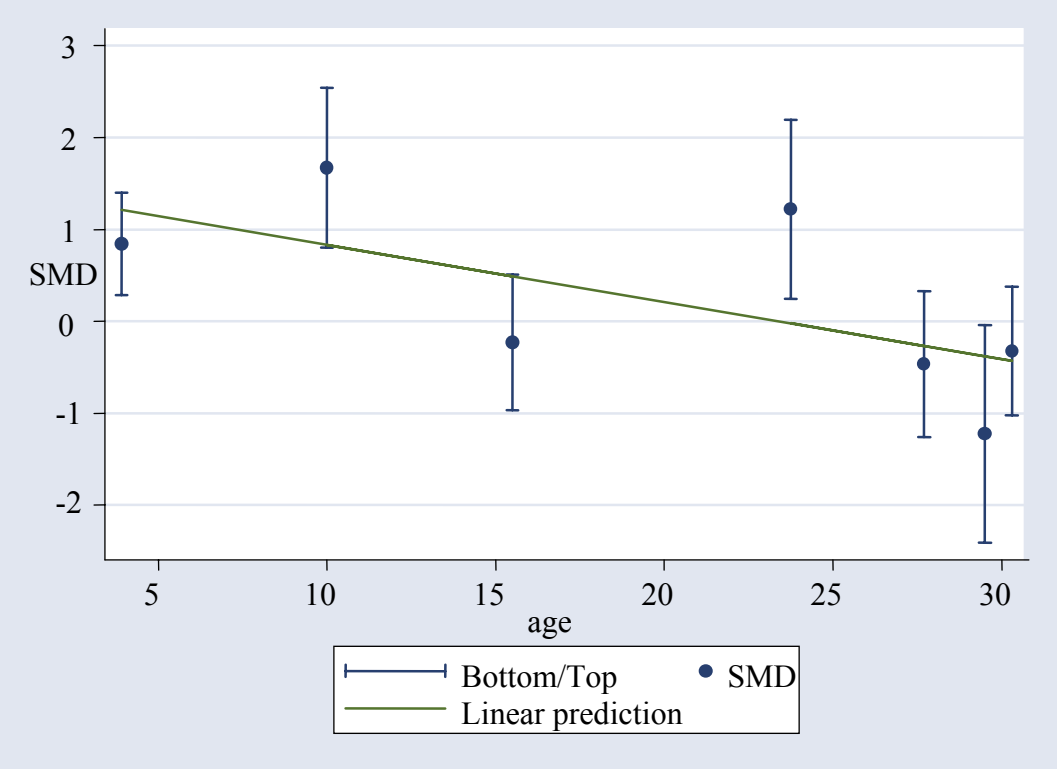

Figure 3.4

Graph of standardised mean difference (SMD) versus mean age of the autistic groups for left amygdala

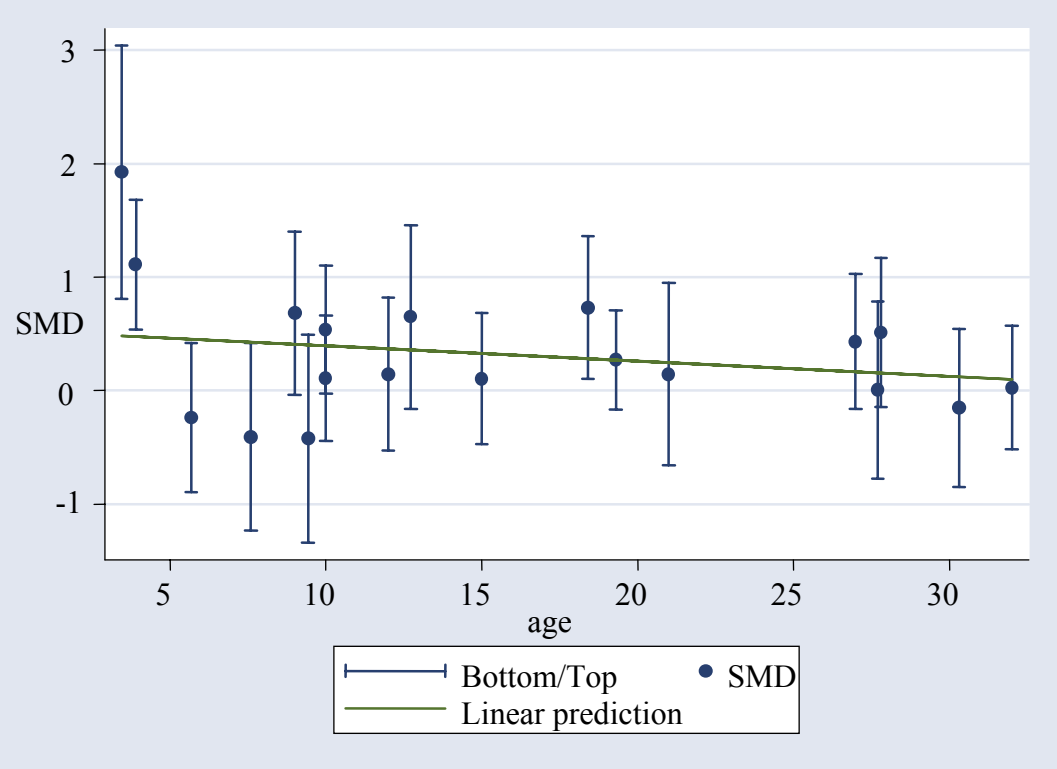

Figure 3.5

Graph of standardised mean difference (SMD) versus mean age of autistic groups for total brain volume

When studies provided data in age stratified subgroups these are entered separately

Evidence of publication bias was found only for the total vermal area (Egger test $p<0{\cdot}01$). Graphical investigation of this result suggests that larger studies found smaller vermal areas in subjects with autism compared to controls whereas smaller studies found the opposite result. However, the small number of studies of this region (n=4) makes interpretation difficult.

Brain regions with insufficient replication to be included in meta-analysis

Data regarding regions of interest which were not examined by sufficient numbers of studies to be included in the meta-analysis are summarised in Tables 3.3-3.8. These tables include studies which were excluded from the meta-analysis and some which were included as they provided data on other regions. Studies which reported area measurements of regions which were included in the meta-analysis as volumes are not discussed.

Enlargements in either grey or white matter are reported for the frontal, temporal and parietal lobes in six out of six, six out of seven and four out of six studies respectively. However, only two out of six studies report occipital enlargements suggesting that this lobe is relatively spared. It is less clear whether grey and white matter compartments are affected equally as the studies show little consistency regarding this. Unfortunately these issues could not be considered in the meta-analysis as the volumes were variously reported for the whole lobes, for grey and white matter in each lobe, for each side separately or as covaried means, meaning they could not be combined. There are indications that within the finding of overall cerebral enlargement specific regions are

affected differently. In particular, differences in asymmetry in brain regions associated with language production, such as the planum temporale and Broca's area, have been reported although the direction of asymmetry differs between studies.[132,138,139] Structural changes in the parahippocampal gyrus[140] and the cingulate gyrus[141] have also been reported although only in one study each.

Two studies address the pattern of cortical folding seen in autism. Hardan et al found an increase in the left prefrontal gyrification index (i.e. greater cortical folding) in children and adolescents with autism relative to normal controls. The same relationship was not seen in adults. They also report a negative relationship between the gyrification index and age in controls which was not seen in subjects with autism.[120] Taking a different approach Levitt et al created maps of major cerebral sulci in autism and examined differences in their location in Talairach space. They reported anterior and superior shiftings of a number of major frontal and temporal lobe sulci.[142]

VBM studies

Four studies used voxel-based morphometry (VBM) and these are summarised in Table 3.9. One of these used single slice 2-dimensional 2D VBM and examined only the corpus callosum finding reductions in both anterior and posterior regions.[143] One study found no differences but considered only 9 individuals,[144] while the other two identified reductions in grey and white matter mainly in frontal and temporal regions.[128,145]

Study (year)	Diagnostic instruments	Autistic Subjects			Control Subjects			Covariates	Main Findings
		N	Mean age	Mean IQ	N	Mean age	Mean IQ		
*Akshoomoff (2004)[106]	DSM-IV, CARS, ADI-R, ADOS	52 (52:0)	6.2	67	15 (15:0)	3.6	-	-	Increased cerebral GM and WM.
**Boucher (2005)[140]	DSM-IV	10 (10:0)	23.8	99	10 (10:0)	24.2	102	-	Reduction in parahippocampal gyrus. No difference in orbital prefrontal or dorsal prefrontal lobes.
*Carper (2002)[108]	DSM-IV, CARS, ADI, ADOS	38 (38:0) *12* *19* *7*	5·7 *3·5* *5·7* *9·4*	- - - -	39 (39:0) *8* *17* *14*	6.5 *3·4* *5·7* *9·3*	- - - -	-	Increased frontal GM and WM, temporal GM and parietal WM in 2-4 year olds. No difference in other lobar volumes or in older children.
Hardan (2004)[120]	ADI-R, ADOS	30 (30:0) *12* *18*	21·8 *12·7* *27·8*	101·8 *104·9* *99·7*	32 (32:0) *13* *19*	21·7 *12·8* *27·7*	105·3 *110·2* *102*	-	Increased left prefrontal gyrification index in subjects under 18 years old. No difference in adults.
Hazlett (2005)[146]	DSM-IV, ADI-R, ADOS	51 (46:5)	2.7	54.1	25 (16:9) *11* *14*	2.5 *2.7* *2.4*	86.3 *58.5* *108.1*	age, gender	Vs low IQ controls – increased GM and WM in all 4 lobes. Vs"normal" IQ controls – increased WM in temporal lobes, and right parieto-occipital lobes, no increases in other regions
Hazlett (2006)[121]	DSM-IIIR, ADI	23 (23:0)	19.1	89.9	15 (15:0)	21.6	102.3	age, IQ	Increased left frontal and temporal GM. No difference in other lobar volumes.
†Herbert (2003)[122]	DSM-III-R, WADIC	17 (17:0)	9	>80	15 (15:0)	-	-	age, tbv, site	Increased cerebral WM.
†Herbert (2004)[147]	DSM-III-R, WADIC	13 (13:0)	9.0	>80	14 (14:0)	-	-	-	Increased "superficial" frontal, temporal, parietal and occipital WM. No difference in "deep" white matter.
**Howard (2000)[99]	DSM-IV	10 (10:0)	23.8	99	10 (10:0)	24.2	102	-	No difference in temporal lobe GM.
Kates (2004)[125]	ABC, ADI-R, ADOS	8 (7:1)	7.6	69.6	16 (14:2)	8.3	123.6	tbv	Reduced frontal, temporal and occipital WM. No difference in other lobar volumes.
Levitt (2003)[142]	DSM-IV, ADI, ADOS	21 (-:-)	10.7	98	20 (-:-)	11.3	114	-	Antero-superior shifting of frontal and temporal sulci

Lotspeich (2004)[127]	ADI-R, ADOS-G	31 (31:0)	11.9	-	21 (21:0)	12.5	-	age, site	Increase in cerebral GM. No difference in WM.
Pierce (2001)[97]	DSM-IV, CARS, ADI, ADOS	6 (6:0)	29.5	83.7	8 (8:0)	28.3	-	-	No difference in fusiform gyrus, inferior temporal gyrus or middle temporal gyrus
Piven (1996)[130]	DSM-III-R, ADI	35 (26:9)	18	91	36 (20:16)	20.2	102.1	-	Increased frontal, temporal and parietal lobe volumes. No difference in occipital lobes.

Table 3.3

Studies of cortical regions with insufficient replication to be included in the meta-analysis (excluding regions involved in speech)

Abbreviations as in Table 3.1

		Autistic Subjects			**Control Subjects**				
Study (year)	**Diagnostic instruments**	**N**	**Mean age**	**Mean IQ**	**N**	**Mean age**	**Mean IQ**	**Covariates**	**Main Findings**
De Fosse (2004)[148]	DSM-IV, ADI-R, ADOS	22 (22:0)	9.4	86.8	11 (11:0)	10.4	114.5	-	Reversal of asymmetry in Broca's area for autistic subjects with language impairment. No difference in planum temporale asymm.
Herbert (2002)[149]	DSM-III-R, WADIC	16 (16:0)	9.0	>80	15 (15:0)	8.3	-	-	Reversal of asymmetry in pars opercularis (associated with Broca's area). Exaggerated asymmetry in planum temporale.
Rojas (2002)[150]	DSM-IV, ADI, ADOS	15 (13:2)	29.9	92.5	15 (13;2)	30.4	119.6	-	Reduction in left planum temporale leading to loss of asymmetry in autism. No difference in right planum temporale or Heschl's gyrus
Rojas (2005)[139]	DSM-IV, ADI, ADOS	12 (12:0)	11.7	95.8	12 (12:0)	11.7	114.5	ipsilateral hemisphere volume	Loss of asymmetry of planum temporale. No difference in Heschl's gyrus.

Table 3.4

Studies of cortical regions involved in speech generation and production in autism

Study (year)	Diagnostic instruments	Autistic Subjects			Control Subjects			Covariates	Main Findings
		N	Mean age	Mean IQ	N	Mean age	Mean IQ		
Boucher (2005)[140]	DSM-IV	10 (10:0)	23.8	99	10 (10:0)	24.2	102	-	Reduction in parahippocampal gyrus.
Hardan (2003)[119]	ADI, ADOS	40 (38:2)	19.3	103.1	41 (39:2)	18.6	104.2	age, wbv	No difference in putamen.
Haznedar (1997)[141]	DSM-IV, ADI	7 (5:2)	24.3	-	7 (5:2)	26.4	-	tbv	Reduced right anterior cingulate area 24'. Increased right anterior cingulate area 25.
Herbert (2003)[122]	DSM-III-R, WADIC	17 (17:0)	9	>80	15 (15:0)	-	-	age, wbv, site	Increased globus pallidus and putamen (non-significant when covary for brain volume). Increased diencephalon. No difference in amygdala-hippocampal complex.
Tsatsanis (2003)[135]	DSM-IV, ADI, ADOS	12 (12:0)	21	106.4	12 (12:0)	18.1	108.8	-	No difference in thalamus volumes in whole group. Reduction in thalamus in the half with larger brains.

Table 3.5

Studies of the basal ganglia, diencephalon and limbic structures in autism

Abbreviations as in Table 3.1

Study (year)	Diagnostic instruments	Autistic Subjects N	Autistic Subjects Mean age	Autistic Subjects Mean IQ	Control Subjects N	Control Subjects Mean age	Control Subjects Mean IQ	Covariates	Main Findings
Egaas (1995)[111]	DSM-III-R, CARS, ADI, ADOS	51 (45:6)	15.5	-	51 (45:6)	15.5	-	-	Reduction in posterior regions of corpus callosum.
Hardan (2000)[117]	ADI, ADOS	22 (22:0)	22.4	100.4	22 (22:0)	22.4	100.5	tbv	Reduction in genu.
Piven (1997)[151]	DSM-III-R, ADI	35 (26:9)	18	91	36 (20:16)	20.2	102.1	gender, IQ, tbv	Reduction in body and splenium.
Manes (1999)[152]	DSM-IV, CARS, ADI	27 (22:5)	14.3	-	17 (11:6)	11.8	-	midsagittal intracranial area	Reduction in genu, rostral body, anterior midbody, posterior midbody and isthmus.
Vidal (2006)[136]	DSM-IV, ADI, ADOS	24 (24:0)	10.0	95.9	26 (26:0)	11.0	104.8	age	Reduction in anterior third

Table 3.6

Studies which provided data on corpus callosum sub-region size in autism

Abbreviations as in Table 3.1

Study (year)	Diagnostic instruments	Autistic Subjects N	Autistic Subjects Mean age	Autistic Subjects Mean IQ	Control Subjects N	Control Subjects Mean age	Control Subjects Mean IQ	Covariates	Main Findings
Hardan (2001)[118]	ADI, ADOS	16 (16:0)	22.2	102.8	19 (19:0)	22.2	101.2	-	No difference in size of lateral ventricles. Increased third ventricle.
Howard (2000)[99]	DSM-IV	10 (10:0)	23.8	99	10 (10:0)	24.2	102	-	Increased lateral ventricles.
Piven (1995)[96]	DSM-III-R, ADI	22 (22:0)	18.4	90.8	20 (20:0)	21.6	103.4	height, IQ	Increased lateral ventricles

Table 3.7

Studies of the ventricular system in autism

Study (year)	Diagnostic instruments	Autistic Subjects			Control Subjects			Covariates	Main Findings
		N	Mean age	Mean IQ	N	Mean age	Mean IQ		
Akshoomoff (2004)[106]	DSM-IV, CARS, ADI-R, ADOS	52 (52:0)	6.2	67	15 (15:0)	3.6	-	-	Increased WM
Allen (2004)[153]	DSM-IV, CARS, ADI-R, ADOS	8 (7:1)	26.9	85	8 (7:1)	26.8	113.8	-	Smaller anterior lobe
Hazlett (2005)[146]	DSM-IV, ADI-R, ADOS	51 (46:5)	2.7	54.1	25 (16:9) *11* *14*	2.5 *2.7* *2.4*	86.3 *58.5* *108.1*	age, gender	No difference in GM or WM compared to either control group
Kates (2004)[125]	ABC, ADI-R, ADOS	8 (7:1)	7.6	69.6	16 (14:2)	8.3	123.6	age, wbv	No difference in GM or WM

Table 3.8

Studies of the cerebellum in autism

Abbreviations as in Table 3.1

Study (year)	Diagnostic instruments	Autistic Subjects			Control Subjects			Notes	Main Findings
		N	Mean age	Mean IQ	N	Mean age	Mean IQ		
Boddaert (2004)[145]	DSM-IV, ADI-R	21 (16:5)	9.3	<70	12 (7:5)	10.8	>70	VBM, temporal lobe SVC	GM reductions in superior temporal sulcus bilaterally. WM reductions in right temporal pole and left cerebellum
Chung (2004)[143]	DSM-IV, ADI-R	16 (16:0)	16.1	>70	12 (12:0)	17.1	>70	2D VBM of corpus callosum	WM reductions in rostrum, genu and splenium
Kwon (2004)[144]	DSM-IV, ADI-R, ADOS	9 (9:0)	14.0	>70	13 (13:0)	13.6	>70	VBM	No differences
McAlonan (2005)[128]	ICD-10, ADI-R	17 (16:1)	12	101	17 (16:1)	11	114	VBM	GM reductions in bilateral orbital and medial frontal gyri, left middle frontal gyrus, right inferior frontal gyrus, right middle frontal gyrus, left middle and superior temporal gyri, right parahippocampal and fusiform gyri, bilateral precuneus and cingulate gyrus, bilateral caudate nucleus and brainstem WM reductions in bilateral cerebellum and internal capsule

Table 3.9

Studies which used VBM to examine neuroanatomy in autism

SVC – small volume correction

Pervasive Developmental Disorder

Studies which examined PDD (as opposed to autism alone) are summarised in Table 3.10. Of these there were 5 which examined only Asperger disorder while the remaining 7 combined individuals with autism and PDD together. Of the studies which considered only Asperger disorder 3 contained region-of-interest data – one for the whole cerebrum;[127] one for the cerebral lobes, cerebellum and basal ganglia;[154] and one gave 2-dimensional length and diameter measurements for the corpus callosum and mesencephalon.[155] Neither of the first two found any significant differences between individuals with Asperger syndrome and unimpaired controls while the last found only a reduction in the anterior-posterior diameter of the mesencephalon. The VBM studies of Asperger syndrome report grey matter reductions in the frontal lobe and both enlargements and reductions in temporal structures.[144,154,156] The remaining studies in Table 3.10 report data for groups containing some individuals with autism and some with other PDDs. A variety of findings are reported including widespread increases in grey matter and reductions in white matter, and an increase in basal ganglia size.

Study (year)	Diagnostic instruments	Subjects (Autism/Asperger/PDD-NOS) N (A/A/P) (M :F)	Mean / median age	Mean IQ	Control Subjects N	Mean / median age	Mean IQ	Covariates	Main Findings
Abell (1999)[156]	DSM-IV	15 (0/15/0) (12:3)	28.8	-	15 (12:3)	25.3	-	-	VBM study Increased GM in left amygdala, bilateral anterior cerebellar lobe, cerebellar vermis, left middle temporal gyrus and right inferior temporal gyrus Decreased GM in right paracingulate sulcus, left inferior frontal gyrus and left occipito-temporal junction.
Hollander (2005)[157]	DSM-IV, ADI-R	17 (9/7/1) (15:2)	28.4	97.1	17 (15:2)	29.4	111.5	tbv	Increased right caudate and total putamen volume
Kwon (2004)[144]	DSM-IV, ADI-R, ADOS	11 (0/11/0) (11:0)	13.5	-	13 (13:0)	13.6	-	-	VBM study Decreased GM in cingulate gyrus and inferior temporal gyrus bilaterally, right entorhinal cortex, right fusiform gyrus, left middle temporal gyrus
Lotspeich (2004)[127]	ADI-R, ADOS-G	21 (0/21/0) (21:0)	12.7	108	21 (21:0)	12.5	114	age, site	No significant difference in cerebral GM or WM
McAlonan (2002)[111]	ICD-10, ADI	12 (0/12/0) (12:0)	32	96	14 (14:0)	33	114	Age, IQ	No difference in total brain, cerebral lobes, cerebellum, basal ganglia or lateral ventricles. Lack of age-related decline in lobar and caudate GM in subjects with Asperger disorder. VBM study GM reductions in fronto-striatal regions; WM reductions in frontal temporal and occipital tracts; WM increases in basal ganglia and uncinate fasiculus
Nieminen von-Wendt (2002)[155]	ICD-10, DSM-IV	28 (0/28/0) (21:7)	22.4	-	28 (21:7)	-	-		Decreased anterior-posterior diameter of mesencephalon

Palmen (2004)[158]	DSM-IV, ADI-R	21 (15/0/6) (19:2)	20.1	114.9	21 (20:1)	20.3	112.6	-	Increased intracranium, total brain, cerebral GM, frontal GM, cerebellum, lateral ventricles and 3rd ventricle
Palmen (2005)[159]	DSM-IV, ADI-R	21 (17/0/4) (21:0)	11.1	106.5	21 (21:0)	10.4	102.5	-	Increased intracranium, total brain, total cerebral GM, frontal, parietal and occipital GM, cerebellum, lateral ventricles and 3rd ventricle
*Salmond (2003)[160]	Clinical Diagnosis	14 (3/11/0) (13:1)	12.9	102.4	18 (6:12)	12.6	-	-	Individual VBM study "Abnormalities" in orbitofrontal cortex (13/14), cerebellum (11/14), superior temporal gyrus (10/14), amygdala (7/14), hippocampus (7/14)
*Salmond (2005)[161]	Clinical Diagnosis, ASAS	14 (3/11/0) (13:1)	12.9	102.4	13 (13:0)	12.1	-	-	VBM study Increased GM in dorsolateral prefrontal cortex, fusiform gyrus, hippocampus, cerebellum, lateral occipitotemporal sulcus, occipital lobe Reduced GM in area adjacent to fusiform gyrus
**Waiter (2004)[162]	DSM-IV, ADI-R, ADOS	16 (-/-/-) (16:0)	15.4	100.4	16 (16:0)	15.5	99.7	-	Increased total brain GM volume No difference in total WM VBM study No significant differences in GM at p corrected level. Trends towards increased GM in left superior and middle frontal gyrus, left middle temporal gyrus, and right medial frontal, cingulate and fusiform gyri
**Waiter (2005)[163]	DSM-IV, ADI-R, ADOS	15 (-/-/-) (15:0)	15.2	100.5	16	15.5 (15:0)	99.7	-	VBM study Right hemisphere - Reduced WM in cingulate, middle and medial frontal, supramarginal and postcentral gyri, extra-nuclear and subgyral regions. Left hemisphere – reduced WM in superior and medial frontal gyri, postcentral gyrus, superior, middle, inferior and transverse temporal gyri, cingulate gyrus, superior parietal lobule, insula and cuneus Reduced WM in isthmus and splenium of callosum

Table 3.10

Region-of interest and voxel-based studies concerning PDD

ASAS – Australian Scale for Asperger syndrome, other abbreviations as in Table 3.1

3.4 Discussion

Methodological Considerations

Most of the studies used reliable methods to ascertain the diagnosis of autism, however many studies considered only male subjects with IQs of over 70. Given that around 70% of individuals with autism are learning disabled[164] and that autism does occur in females (although less commonly than in males) the available literature is thus not representative of the general clinical population. Most of the study groups were well matched for age, gender and IQ, the exceptions being some studies which examined people with autism and low IQ. In these the control groups were often of higher IQ than the cases. The lack of an IQ matched control group risks introducing error as the groups differ on both IQ and clinical status, rather than clinical status alone.

While the vast majority of reviewed abstracts were written in English there were four non-English studies excluded which, judging from the abstracts, may have met inclusion criteria and it is possible that this may affect the results. However, the effect of this may be minimised by the inclusion of several studies which were published in English but were carried out in non-native English speaking countries such as Norway and Japan. Perhaps more importantly several papers were excluded from the meta-analysis as they did not present raw data and others were excluded as they combined autistic individuals with those suffering from other pervasive developmental disorders. In addition, as can be seen from Tables 3.3 -3.8, a considerable amount of data was excluded regarding regions for which insufficient numbers of publications were available. While these data are

worthy of some consideration further replication is required before firm conclusions can be made.

Main findings and clinical implications

Consistent evidence was found for an increase of the total brain volume, the cerebral hemispheres and the cerebellum in autism. In addition, an increase in the volume of the caudate nucleus was seen whereas the corpus callosum was reduced in size. Reductions in the size of the midbrain and the cerebellar vermal lobules VI-VII and VIII-X were also found although with significant heterogeneity. For vermal lobules VI-VII this heterogeneity was related to the age and IQ of the study population. While no difference in size was found for the amygdala a significant effect of age on the data was apparent.

The consistent finding of cerebral enlargement is in keeping with those post-mortem studies of autistic individuals which have reported megalencephaly, cortical thickening and an increase in cerebral neuronal density.[165] Increased numbers of smaller and less dense cortical minicolumns (vertical chains of cells extending through the cortical layers thought to be functional sub-units of cortex) have also been reported at post-mortem.[166] A larger less well organised cerebral cortex has been hypothesised to lead to inefficient connectivity and less integration of dispersed brain regions, a view supported by a variety of functional neuroimaging studies.[167] The reduction in the cross-sectional area of the corpus callosum indicates that inter-hemispheric connectivity is also likely to be less efficient in autism and there is evidence from neuropsychological tests that this is indeed the case.[168] Furthermore the enlargement of the cerebellum is likely to further affect the

co-ordination of brain activity. Previously regarded as being solely involved in motor activities, it is now known that the cerebellum also connects to cortical regions involved in emotional and cognitive functions and it is thought to play a similar role in these domains as in the regulation of motor function.[169,170] A lack of integration and regulation of distributed brain functions could lead to deficits in complex processes which require the recruitment of a variety of brain regions, such as language and social behaviour.[167]

An increase was also found in caudate volume, without evidence of heterogeneity. This finding was also recently reported in a study of individuals with autistic spectrum disorders in which the size of the caudate was found to correlate with the degree of restricted, repetitive behaviours.[157] Previous findings of enlarged caudate volume and abnormal perfusion of fronto-striatal-thalamic structures in obsessive compulsive disorder lend further, albeit indirect, support to this result.[171] It is therefore likely that caudate enlargement in autism is linked to an intrinsic abnormality of neuronal circuitry although it is possible that the use of antipsychotic medications, which have been associated with caudate enlargement,[172] may be confounding the findings. Unfortunately, there was not enough information in the original reports to discern whether or not those with autism were receiving psychotropic medications, let alone to examine any potential dose relationship.

Effect of confounding variables

The midbrain and lobules VIII-X of the vermis were found to be reduced in size but with significant heterogeneity which was not explained by age or IQ. These findings should

therefore be interpreted with great caution. Lobules VI-VII of the vermis were also reduced in size and the heterogeneity of this finding was at least partly accounted for by differences in the age and IQ of the study population. As can be seen in Table 3.1 the case and control groups for this region were generally well matched for age. The significant finding for age therefore represents a change in the difference in vermal size between the groups as they grow older, i.e. there may be a different growth trajectory for this region in autistic individuals as compared to controls which produces a normalisation of size with increasing age (Figure 3.2). The largest single study of this region, which included 98 autistic individuals, found a similar relationship with age to that which identified in the meta-regression.[87] While this study contributed 9 data points to the meta-regression the result remained significant even when these were pooled to give one mean value showing the findings are not driven solely by this study. With respect to IQ, the lower the IQ of the autistic groups the less well matched they were to the control groups which tended to be of average IQ. Therefore the significant finding for IQ indicates that as the IQ *differences* between the groups lessen so do the volumetric differences (Figure 3.3). Taken together these findings indicate that younger autistic individuals show real reductions in the size of vermal lobules VI-VII whereas those identified in older individuals may be an artefact of IQ differences between case and control groups.

Age was also found to have a significant effect on the results for the amygdala with younger autistic individuals showing enlargements which are not present in older groups. Functional imaging studies indicate that the amygdala is involved in social cognition, in

particular empathy and "theory of mind" (the ability to attribute mental states to others).[173] It has been shown that lesions in childhood are especially likely to lead to theory of mind impairments.[174] Deficits in social cognition are characteristic of autism and the early structural abnormality of the amygdala reported is likely to play a key role in the development of such impairments.

No statistically significant relationship was found between age and effect size for total brain volume, a result which appears to contrast with that of a previous meta-analysis of MRI and head circumference studies by Redcay and Courchesne.[137] They found that brain volume enlargements are apparent in young children in the first 4 years of life but normalise following this period. The difference between the two meta-analyses is the inclusion of head circumference studies in infants under 2 years old as a proxy for brain volume in the Redcay and Courchesne report. It is possible that the current study did not find an age-brain volume relationship due to a lack of MRI studies in these very young autistic individuals. Certainly the two studies in the current meta-analysis pertaining to subjects around 4 years old show markedly greater effect sizes when compared with those of older children and adults (Figure 3.5).

Additional Information from Qualitatively Reviewed Data

In general caution is advised in interpreting the results for regions which were not included in the meta-analysis and until there is replication of many of the findings they should be regarded as preliminary. In general frontal and temporal regions appear to be the most consistently identified as abnormal by ROI, VBM and studies of cortical

folding. These regions are particularly involved in executive function, social behaviour and language all of which are disturbed in autism. The abnormal asymmetry in language regions reported by a number of studies suggests that a disturbance of lateralisation may be relevant in autism. Further evidence for this is provided by findings of increased rates of mixed-handedness in autism.[175] The structural changes reported for the parahippocampal gyrus and the cingulate gyrus along with post-mortem reports of increased cell packing density in the cingulate cortex[176] suggest that abnormalities of the limbic system beyond those found in the amygdala may also be important in the pathogenesis of autism.

Studies concerning PDD

It is difficult to interpret the findings of those studies which examined PDD due to the tendency of researchers to combine subjects with autism and those with other PDDs together. The status of these PDDs in relation to autism is unclear and it is not known whether they share similar neuroanatomical features. Those studies which have directly compared Asperger syndrome with autism have found some neuroanatomical differences between the two suggesting that it may not be wise to combine them for study.[127,144] It is therefore possible that the findings of such studies will depend upon the relative proportions of subjects with autism to those with other PDDs. For example, the two studies by Palmen et al concern mainly individuals with autism and are thus likely to primarily reflect the neuroanatomy of autism as opposed to that of other PDDs.[158,159] Of the studies which examined Asperger syndrome alone the ROI studies tended to find no volumetric differences whereas the VBM studies detected tissue density differences in

the frontal and temporal lobes (although not necessarily in the same direction). This suggests that if the brain is different in Asperger disorder this is more subtle than is seen in autism although more research is required to confirm this.

Concluding Remarks

On the basis of the existing literature, we can conclude that autism is associated with enlargements of the cerebral hemispheres, the cerebellum and the caudate nucleus; with reductions in the size of the corpus callosum and possibly the midbrain and vermal lobules VI-VII and VIII-X. In addition the vermal lobules VI-VII and the amygdala may show unusual growth trajectories. Within the cerebrum the frontal and temporal lobes appear to be most affected, in particular language related areas. Thus the cardinal features of the disorder may result from a combination of a global lack of integration and regulation of dispersed brain regions and more specific abnormalities in particular structures.

Chapter 4

Introduction to Experimental Section

4.1 The Edinburgh Study of Comorbidity

The Edinburgh Study of Comorbidity (ESC) is a large, ongoing prospective study which was designed to identify and investigate a group of adolescents at high risk of developing schizophrenia by virtue of being cognitively impaired. There is a well established association between schizophrenia and cognitive impairment.[177] Reductions in cognitive functioning compared to normal controls have been reported both prior to and after the onset of illness.[178-180] Despite this the majority of individuals with schizophrenia have IQs in the unimpaired range. However, among the learning disabled population (people with an IQ of less than 70) there is an excess of schizophrenia with prevalence rates being three times greater than those in non-learning disable people.[181] Research which has examined adults who are comorbid for learning disability and schizophrenia has shown that such individuals more closely resemble non-learning disabled adults with schizophrenia rather than non-schizophrenic learning disabled adults in terms of brain structure. This suggests that the cause of the learning disability in the comorbid group is in fact severe schizophrenia. In turn this raises the possibility that within a population of adolescents with learning disability there are some whose learning disability is the result of a psychotic illness which is yet to become manifest.[182] This premise is key to the design of the ESC.

As important to the design of the ESC are the results from the Edinburgh High Risk Study (EHRS) which show that within a population of individuals who are at high risk of developing schizophrenia by virtue of genetic reasons, it is possible to predict those who

will go on to develop schizophrenia using easily administered rating scales of behaviour (the Childhood Behaviour Checklist (CBCL))[183] and schizotypal features (the Structured Interview for Schizotypy (SIS)).[184] These findings allow the identification and detailed investigation of subjects who have the highest risk of developing schizophrenia by virtue of being not only cognitively impaired but also because they display the behavioural symptoms and schizotypal features which predicted the development of schizophrenia in the EHRS. Clearly the ESC rests on the assumption that the two high risk populations (the genetic high risk population in the EHRS, and the cognitively impaired high risk population in the ESC) will prove to show similarities in terms of the pattern of illness development.

Due to the overlap of schizotypal and autistic features, it was recognised that a number of subjects with autistic features would also be recruited into the ESC. Thus a measure of autistic features (the Social Communication Questionnaire (SCQ))[185] was also included in the design of the study.

4.2 The Current Study

What follows is an examination of the brain structure associated with schizotypal and autistic features in the baseline sample acquired for the Edinburgh Study of Comorbidity (ESC). This unique sample allows a number of important issues to be addressed. Firstly, as discussed in Chapter 3 the existing research on PDD focuses mainly on high-functioning individuals despite the fact that this is not representative of the populations seen clinically who are primarily of low IQ. In addition those that have studied low IQ autism have tended to use control groups of individuals with IQs in the normal range leaving the possibility that any results identified relate to IQ differences rather than autistic features. In the following study autistic features are studied across a wide range of IQ with a developmentally appropriate control group in addition to an unimpaired control group. No previous research has studied the neuroanatomy of schizotypal features in individuals with learning disability, despite the high prevalence of schizophrenia in this group, therefore the clinical and neuroanatomical features of this group are considered here. Finally the ESC allows a comparison between schizotypal and autistic features with respect to neuroanatomical measures and an examination of individuals who are comorbid for both conditions.

The emphasis is on the current status of participants and not their future likelihood of developing schizophrenia. In this context the CBCL is of limited usefulness due to its lack of specificity with respect to diagnosis therefore it is not considered further. However the SIS allows the identification of subjects with significant degrees of

schizotypy, while the SCQ scores can be used to identify those with autistic features. The neurostructural measures examined are the size of the whole brain, prefrontal lobe, corpus callosum and the degree of prefrontal cortical folding. Each of these measures has been seen in the relevant literature reviews to be abnormal in ASD and/or schizotypy. Before continuing it is useful to consider each measurement in detail, with the exception of the whole brain volume.

The Corpus Callosum

The corpus callosum is the largest white matter tract in the human brain and serves interhemispheric communication between homologous cortical areas. Development begins early in gestation and proceeds in an anterior-posterior direction. An exception to this is the rostrum which develops last and folds under the anterior callosum or genu.[186] In utero the growth of the corpus callosum is primarily due to the addition of axons. All of the callosal axons are in place by the time of birth – there is no evidence to suggest axonal addition postnatally. Primate studies have shown that immediately following birth the corpus callosum has many more fibres than are present in the adult brain. Around 70% of these fibres are eliminated in the first 3 postnatal months at rates of up to 50 fibres per second.[187] Despite the lack of axonal addition after birth, the midsagittal area of the corpus callosum continues to grow, particularly in the first few years of life.[186] Growth continues at a slower rate throughout childhood and adolescence particularly in the posterior and middle corpus callosum with the anterior regions remaining largely unchanged.[188] It is likely that the postnatal growth of the corpus callosum is primarily due to the myelination of fibres.

Axonal fibres in the corpus callosum are topographically organised such that the different sub-regions contain axons from different areas of the cortex (see figure 5.2).[189] Abnormalities in sub-regions may therefore reflect irregularities deriving from relatively specific cortical areas. Given that the midsagittal area of the corpus callosum correlates with the number of decussating fibres,[190] changes in this area should provide information regarding the number of neurones from which the fibres originate. Thus the corpus callosum provides a useful index through which to examine for regional size differences in the cerebral cortex. However, as discussed above, postnatal growth of the callosum is primarily due to fibre myelination therefore disturbances to this process may also affect the measured callosal size. Examining the relationship between regional cortical grey matter and the relevant callosal sub-region may help to clarify whether callosal size differences relate to myelination or change the number of axons.

The Prefrontal Lobe

The prefrontal lobe is the most anterior part of the human brain and lies in front of the motor and premotor areas of the frontal lobe. It is defined by the presence of a prominent cell layer IV (granular layer) and is divided into three neuroanatomical regions – lateral, medial and orbital. In typically developing humans the prefrontal lobe grey matter increases in size from birth until around the age of 12 when it begins to gradually decrease. In contrast the white matter compartment continues to grow into late adolescence and early adulthood due to axonal myelination.[191] Comparative studies have shown that the prefrontal lobe makes up a disproportionate amount of the human brain

relative to other mammals (29% as compared to 17% in chimpanzees, 12.5% in dogs and 3.5% in cats).[192] This expansion of the prefrontal lobe is assumed to parallel the evolution of higher order cognitive functions.

The study of prefrontal lobe function and dysfunction effectively began with the case description of Phineas Gage. A railway worker who sustained a penetrating injury to the prefrontal region, Gage was described by his physician as

> "fitful, irreverent, indulging at times in the grossest profanity (which was not previously his custom), manifesting but little deference for his fellows, impatient of restraint or advice when it conflicts with his desires, at times pertinaciously obstinate, yet capricious and vacillating, devising many plans of future operations, which are no sooner arranged than they are abandoned in turn for others appearing more feasible."[193]

Unable to plan his actions or limit his behaviour Gage displayed some of the classic signs of frontal lobe dysfunction. Subsequent lesion studies and, more recently, functional MRI studies have provided further insights into the functional neuroanatomy of the prefrontal lobe. Broadly speaking the lateral prefrontal region is involved in working memory and preparatory set the intact functioning of which are essential for effective planning and sequencing of thought and behaviour; the medial region is involved in drive and motivation; and the orbital region in impulse control and response inhibition. All three regions are involved in aspects of attention.[192] Subtle impairments in all these domains have been hypothesised to relate to the behavioural symptoms and cognitive dysfunction observed in psychiatric disorders such as schizophrenia and autism.

The Gyrification Index

The gyrification index is a widely used measure of the degree of cortical folding. Initially lissencephalic (smooth) the human brain begins to fold at about 20 weeks gestation to form ridges or gyri which are separated by indentures or sulci. The first sulci to appear are called primary sulci and are remarkably consistent in their placement between individuals. Examples of primary sulci include the Sylvan fissure and the calcarine sulcus. Branches of primary sulci are called secondary sulci while those of secondary sulci are called tertiary sulci. These are less deep and more variable in their position between individuals. Secondary sulci are all present by birth whereas tertiary sulci continue to form in the first year postnatally.

Both genetic and environmental factors appear to be important in determining the ultimate pattern of cortical folding. A complete failure of cortical folding results in lissencephaly which is associated with mutations in genes such as LIS1 and DCX.[194] Specific genetic disorders such as Williams syndrome (7q11.23 deletion) are known to be associated with a global increase in gyrification[195] and with an anomalous course of the Sylvan fissure.[196] Additionally in normal individuals gyral patterns have been shown to be more concordant in monozygotic rather than dizygotic twins.[197] However, in the latter study the heritability of gyral patterns was much less than that found for brain volume suggesting that environmental agents have a major role to play in cortical folding. Among the environmental factors implicated in disturbances of cortical folding are infection,[198] and hypoxia due to placental insufficiency.[199]

The exact mechanisms through which these aetiological factors produce convolutions of the cerebral cortex are unknown. Brain growth is certainly important with the earliest theories of gyrification suggesting that folding of the cortex was a result of cerebral expansion constrained by the limited space available in the intracranial vault.[200] The disordered layering of the cortex in lissencephalic brains has led others to suggest that folding results from differential growth of cortical layers with outer layers growing faster than inner ones and the resulting mechanical tension leading to buckling of the surface.[201] Research also suggests that cortico-cortical and subcortico-cortical connectivity have important roles to play in determining the eventual pattern of cortical folding.[202-204] It has been suggested that cortical regions with many connecting fibres are drawn closer to each other to form a gyrus by the mechanical tension produced by the fibres. Certainly connectivity between areas in the same gyrus has been found to be greater than that between areas separated by a sulcus.[202] Others have emphasised that disruption of thalamo-cortical fibres leads to an increase in cell death in the developing cortex therefore variations in thalamo-cortical connectivity will contribute to differential cortical growth and hence regional folding.[203,204] Dysconnectivity has been suggested as pertinent in the study of both autism[205] and schizotypy[84] hence the relevance of studying the gyrification index in these syndromes.

4.3 Hypotheses

Examination of schizotypy

Clinical Features

The schizotypal subjects will have a higher prevalence of clinical features consistent with schizophrenia spectrum disorders, in particular delusions and hallucinations

Neuroanatomical Measures

Compared to the control groups the schizotypal subjects will show:

1) increased right prefrontal lobe volume

2) increased right prefrontal gyrification index

3) increased midsaggital area of the genu of the corpus callosum

4) decreased midsagittal area of the isthmus of the corpus callosum

Examination of PDD

Clinical Features

The PDD subjects will have a higher rate of clinical features consistent with autism spectrum disorders, in particular anxiety, obsessive-compulsive phenomena, slowness and affectual flattening.

Neuroanatomical Measures

Compared to the controls, those with PDD will show:

1) increased whole brain volume

2) increased prefrontal lobe volume

3) increased left prefrontal gyrification index

4) reduced midsaggittal area of the corpus callosum

Examination of comorbidity of schizotypy and PDD

Clinical Features

In line with the idea that among the PDD population there is a group of individuals who have features of PDD due to a primary diagnosis of schizotypy, it is hypothesised that those comorbid for PDD and schizotypal features will show clinical similarities to the those with schizotypal features alone but will differ from those with PDD alone.

Neuroanatomical Features

A similar pattern is expected to that hypothesised for the clinical features, i.e. the comorbid groups are expected to differ in terms of the brain structural measures from those with PDD alone but be comparable to those with schizotypy alone.

Chapter 5

Methods

5.1 Recruitment

The recruitment process is summarised in figure 5.1. Recruitment was via schools and colleges across 18 out of the 19 Educational Authorities in Scotland which are within reasonable travelling distance of Edinburgh (one Educational Authority declined to participate). Of the 273 schools and colleges approached 99 agreed to enter the study. The head teachers of these schools were asked to identify adolescents receiving special educational assistance, in particular those with a presumed IQ in the range 50-80. Exclusion criteria at recruitment were known syndromic learning disability, severe cerebral palsy, profound learning disability, lack of speech and a known brain injury.

Parents of the adolescents identified were then invited to participate in the study by letter. Five hundred and one individuals initially agreed to participate although 64 of these subsequently withdrew and a further 42 were excluded on the basis of the criteria above leaving a total of 395 subjects. 394 of the 395 were assessed using the Structured Interview for Schizotypy (SIS)[184] and the Childhood Behavioural Checklist (CBCL)[183] (one participant did not complete the SIS). Cut-offs on these scales, which were found to predict the later development of schizophrenia in the Edinburgh High Risk study,[206] were used to identify those suitable for recruitment into the next phase of the study for more detailed assessment. The average scores on the SIS and the CBCL were higher in this population than in the Edinburgh High Risk Project therefore the cut-off points were scaled up appropriately. Participants were evenly sampled into 4 groups based on these cut-offs – $SIS_{high}CBCL_{high}$, $SIS_{high}CBCL_{low}$, $SIS_{low}CBCL_{high}$ and $SIS_{low}CBCL_{low}$. In

addition to the subjects receiving special educational assistance a control group consisting of the siblings of subjects and young people from the same environment was also recruited. The controls had no history of receiving educational assistance or of major psychiatric disorder.

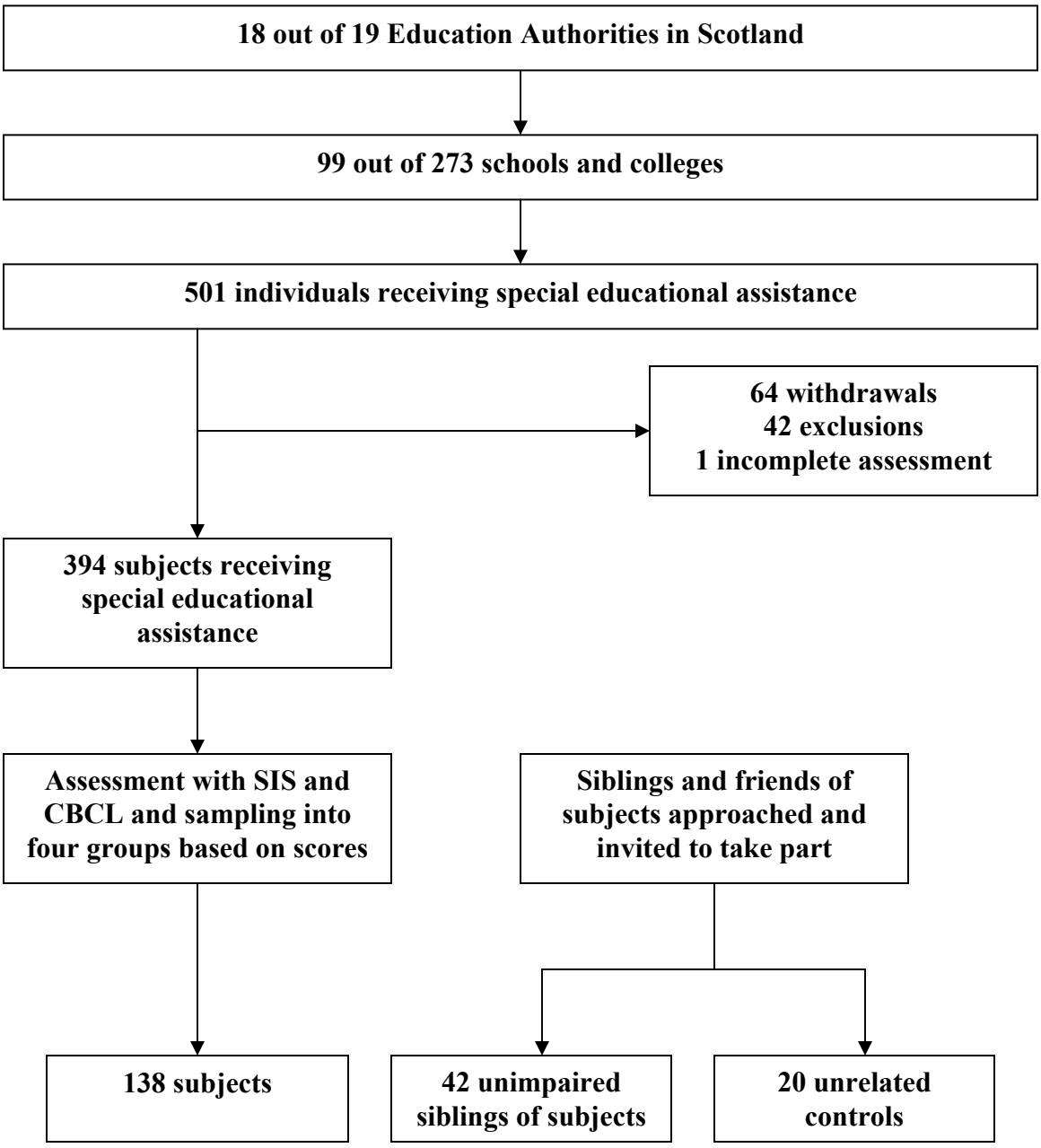

Figure 5.1

Summary of the recruitment process

The current report concerns the baseline data of the first 200 participants who underwent the detailed clinical, neuropsychological and neuroimaging assessments. They consist of 138 individuals receiving special educational assistance, 42 sibling controls and 20 unrelated controls. On IQ testing it was revealed that two of the unrelated controls had IQs of less than 70 (65 and 69) therefore they were excluded from the study. In addition 4 sibling controls and 1 unrelated control were excluded as they scored above the cut-off for the SIS. Thus the final number of participants considered in the study is 193 - 138 adolescents in special education, 38 unimpaired siblings and 17 unrelated, unimpaired individuals. In order to limit the number of comparisons the siblings and the unrelated controls were combined to form one unimpaired control group, with relationships between the subjects and controls being accounted for in the analysis (see Section 5.5).

5.2 Assessments

The Structured Interview for Schizotypy (SIS)

The SIS is an observer rated interview schedule developed by Kendler and validated in three separate pilot studies where it was found to reliably distinguish between the relatives of patients with schizophrenia and relatives of controls.[184] It is divided into two main sections – "symptoms" and "signs"; the former takes the form of a semi-structured interview while the latter is rated by the investigator following the interview and encompasses the observed behaviour of the subject. The items covered in the "symptoms" section are social isolation/introversion, sensitivity, social anxiety, ideas of reference, suspiciousness, restricted emotion, magical thinking, illusions, psychotic-like symptoms, derealisation/depersonalisation, adult antisocial traits, irritability and impulsivity. Adult antisocial traits was excluded from the current study as the majority of the participants were not of sufficient age to be rated. The main items rated in the "signs" section are rapport, affect, organisation of speech/thought, odd/eccentric behaviour and suspiciousness. Individual scores are assigned to each question and a total score is generated. In addition, the investigator allocates a global score of between 1 (marked) and 7 (absent) for each section listed above. The cut-off in the current study relates to a composite score derived from each of the individual sections. As described above, this cut-off is derived from the results of the Edinburgh High Risk study and modified to reflect the generally higher SIS score in intellectually impaired populations. It is important to note that the cut-offs while empirically derived, are not diagnostic of a particular disorder, nor are all those who score above the cut-off likely to develop

schizophrenia; rather it acts simply to allow comparisons to be made between two groups with different degrees of schizotypal features.

The Social Communication Questionnaire (SCQ)

Originally named the Autism Screening Questionnaire the SCQ was developed due to the perceived need for a reliable and valid screening instrument for autistic spectrum disorders.[185] It is based on the revised version of the Autism Diagnostic Interview (ADI-R), one of the most widely accepted standardised diagnostic parental interviews for autism. The SCQ is not a diagnostic interview but is completed by the primary caregiver themselves in the form of a questionnaire. There are 40 questions answered in a yes/no format which are divided into two sections. The first covers present behaviours while the second relates to the time when the subject was around 4-5 years old. The questions cover the three main areas which make up the diagnostic criteria for autism - reciprocal social interaction, language and communication, and repetitive and stereotyped patterns of behaviours. Each question scores one point, giving a maximum total of 40. The SCQ was validated in a population of 200 individuals with a variety of neurodevelopmental disorders including autism, other pervasive developmental disorders (comprising atypical autism, Asperger syndrome, Fragile X and Rett syndrome) and a variety of other disorders which may share some features with autism and which it would important to distinguish from autism (such as developmental language disorder, attention deficit hyperactivity disorder, learning disability and anxiety disorders). Two cut-off points were derived from this study. The first (15/40) is used to distinguish individuals with any pervasive developmental disorder from individuals with other disorders, while the

second, higher cut-off (22/40) is used to sub-divide the PDD group into those with PDD-NOS and those with autism.[185]

The Clinical Interview Schedule

The Clinical Interview Schedule (CIS)[207] is a semi-structured interview covering a wide range of psychiatric symptoms and signs which are rated on a 5 point scale from 0 (absent) to 4 (severe). Scores of 2 or more are generally regarded as indicating morbid levels of symptomatology. In the current study the modified version which allows for the sub-classification of psychotic phenomena was used.[208] It is divided into 2 sections – reported symptoms and manifest abnormalities. In the first the interviewer rates the subject on their own account of the frequency, duration and intensity of any symptom in the past week. The subjects account is taken at face value with the investigators interpretation of the symptoms discounted. In the second section, manifest abnormalities, the interviewer is expected to apply their clinical judgement in making assessments about the subject for each item. Section 1 includes somatic symptoms, excessive concern with bodily functions, fatigue, sleep disturbance, lack of concentration, irritability, depression, depressive thoughts, elation, anxiety, phobias, obsessions and compulsions, and depersonalisation. Section 2 includes observed slowness, suspiciousness, histrionic behaviour, depression, agitation, elation, flattening of affect, delusions, hallucinations, incongruity of affect, incoherence of speech and poverty of speech.

5.3 Division of Subject Groups

In order to examine the clinical and brain structural characteristics of the participants with respect to autistic and schizotypal features the subject group was initially considered as a whole but then divided into groups depending on their scores on the SIS and the SCQ. For each scale there is a group of subjects receiving special educational assistance who do not score above the cut-offs. In the analyses which follow these subjects form a second control group which can be considered analogous to "psychiatric" control groups sometimes used in other research. The term "educational" controls is used to describe this group. It should be noted that the educational controls will differ depending on what scale has been used to divide the subject group. For each analysis the same group of unimpaired controls is used.

Division of subjects based on SIS

The SIS cut-off divides the subjects into two groups – those above the cut-off (hereafter referred to as SIS+) and those below the cut-off (educational controls) as well as the unimpaired controls. The demographic characteristics of these groups can be seen in the appropriate section of the results (Table 6.3).

Division of subjects based on SCQ

The SCQ cut-offs distinguish three groups – autism, PDD-NOS and subjects who show no signs of PDD. Thus this section concerns 4 groups – autism, PDD-NOS, educational controls and unimpaired controls. It should be noted that no SCQ result was available for

three of the subjects as they were either adopted after the age of 5 or in foster care. The demographic characteristics of the SCQ groups can be seen in the appropriate results section (Table 6.6)

Division of subjects based on both SIS and SCQ

In an attempt to examine issues of comorbidity between schizotypal and autistic features the subjects were split into 6 groups as shown in Table 5.1 and the unimpaired controls. The demographic characteristics of these groups are also shown in the appropriate section of the Results (Table 6.9).

		Group determined by SIS	
		SIS+	*SIS-*
Group determined by SCQ	*Autism*	Comorbid Autistic	"Pure" Autistic
	PDD-NOS	Comorbid PDD-NOS	"Pure" PDD-NOS
	Non-PDD	"Pure" SIS+	Educational Controls

Table 5.1

Division of subject groups to examine comorbidity

5.4 MRI scanning

Acquisition

MR imaging was performed at the SHEFC Brain Imaging Research Centre for Scotland on a 1.5T GE Signa Echospeed system (GE Medical Systems, Milwaukee, Wisconsin) operating in research mode consisting of a T1-weighted sagittal sequence with parameters of 16/450/0.75 (TE/TR/excitations) and a T2-weighted axial sequence with parameters of 102/6300/2. Volume data was obtained with a 3D inversion-recovery prepared T1-weighted sequence with parameters of 3.3/8.1/1, TI 600, flip 15, slice thickness 1.7 mm (no gap), matrix 256×192, FOV 220 mm.

Whole Brain Volume

The whole brain volume was derived using a semi-automated method. SPM 99 procedures were used to recover a native space brain tissue mask for each brain.[209] These tissue masks were dilated to recover whole brain volumes inclusive of cortical and sub-cortical CSF. The dilation process, implemented in a Matlab function, was allowed to overrun and these over-dilated brains were hand edited using Analyze 5.0 to give the brain volumes upon which the analysis was based. The final whole brain volume consisted of the total grey and white matter excluding ventricular CSF. On average each brain required around 1 hour to extract.

Corpus Callosum

To account for inter-individual differences in the exact location and orientation of the head when scanning, images were reformatted using a standardised method.[210] The midpoints of the anterior and posterior commisures were identified on the most superior axial slice on which they were visible. A third point superior to the anterior commisure lying in the interhemispheric fissure was then identified and the images were resectioned using the plane formed by these three points as the midsagittal slice. The corpus callosum was outlined on this slice and divided into 7 sub-regions as outlined by Witelson[189] and shown in Figure 5.2 with the corresponding cortical regions in brackets. The average parcellation time for the corpus callosum was 15 minutes per scan.

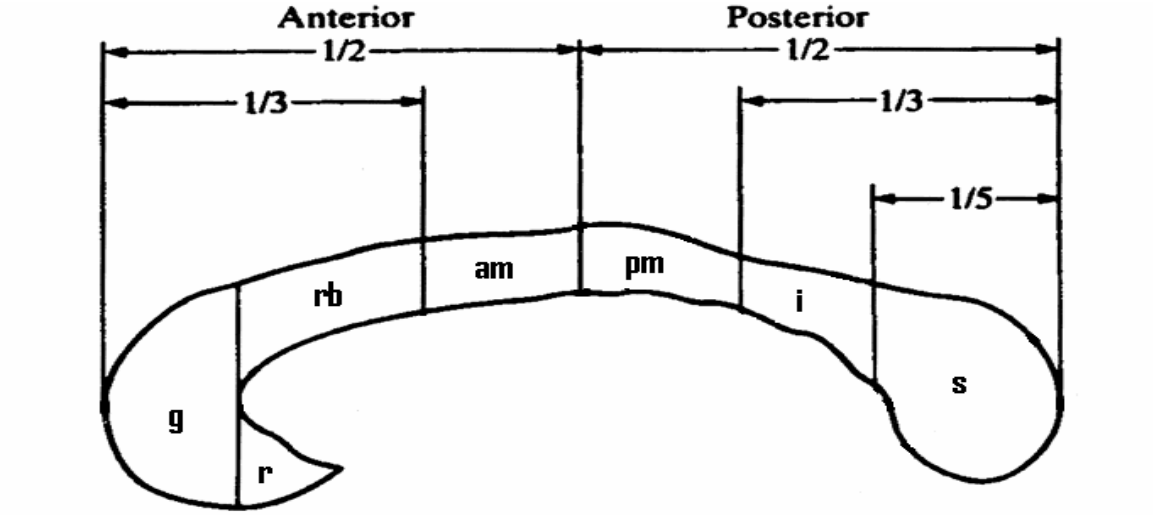

Figure 5.2
Corpus Callosum subdivided as per Witelson (1989)[189]
Sub-regions labelled as below with corresponding cortical region in brackets
r = rostrum (orbital prefrontal, premotor), g = genu (prefrontal), rb = rostral body (premotor, supplementary motor), am = anterior midbody (motor), pm = posterior midbody (somaethetic, posterior parietal), i = isthmus (superior temporal, posterior parietal), s = splenium (inferior temporal, occipital)
Adapted from Hardan et al (2000)[117]

Prefrontal Lobe Volumes and Gyrification Index

The prefrontal lobe volumes and gyrification index were determined using the previously extracted whole brains and applying a new automated method which allows the computation of the gyrification index (aGI).[211] The posterior limit of the prefrontal lobe was the first coronal slice in which the genu of the corpus callosum becomes visible moving caudally. Normally the aGI tool detects this slice automatically however this was not possible in this cohort, probably as a result of reduced white matter integrity of the corpus callosum, therefore it was set manually.

Briefly, the aGI tool works through several stages. First, the previously extracted whole brains are preprocessed using SPM 99 functions. They are segmented into grey and white tissue, reorientated in native space along the AC-PC axis and resliced to give voxels of size 1mm x 1mm x 1mm. Next the tool reads in the manually set anterior limit of the corpus callosum and detects the interhemispheric fissure thus splitting the lobes. The inner contour is then traced along the entire surface of the brain including into each sulci. Buried sulci (i.e. those that do not communicate directly with the cortical surface on that particular slice) are also included. The outer contour, in accordance with Zilles et al (1988),[212] is determined by rounding the exposed surface of the brain, essentially filling in the troughs between gyral peaks, and measuring this rounded contour. The results are then exported and the gyrification index calculated by dividing the inner by the outer contour. The prefrontal grey and white matter volumes derived from the SPM segmentation algorithm used in the preprocessing step are also recovered.

Figure 5.3
Example of an aGI trace

Reliability Studies

Two investigators carried out the tracing of the whole brain volume and the corpus callosum. For the purposes of establishing intra-rater reliability each investigator traced ten randomly selected scans twice. A further twenty scans were traced by both investigators (10 at the beginning of the study and 10 at the end) to establish inter-rater reliability. The intra-class correlation coefficients were calculated and ranged between 0.8 (rostrum) and 1.0 (whole brain volume).

5.5 Statistical Analysis

All statistical analyses were carried out using SPSS 14.0 for Windows. There were four parts to the analysis. Part 1 considered the subjects in special education as a whole; part 2 examined the subject groups formed by the SIS cut-offs; part 3 concerned autistic features using the groups determined by the SCQ cut-offs; part 4 examined comorbidity and concerned the groups derived by using by the SIS and the SCQ to divide the subjects. In all analyses concerning neurostructural measures the effects of age and gender were controlled for. IQ was included as a covariate in part 1 but not in parts 2-4 as the use of the educational control group accounted for IQ. When the unimpaired control group was included in the analysis the sibling relationships between subjects and controls were accounted for by the use of a pedigree variable which is essentially an identifier allocated to each family group. When analysis of covariance (ANCOVA) was used standardised residual plots were checked to ensure the appropriateness of the test. As there is little known about this population group so that this study is of a preliminary nature no attempt has been made to correct for multiple comparisons.

Part 1 – All subjects in special education

The correlation between the SIS and the SCQ was examined using Pearson's r then relationships between the neurostructural measures and the SIS and SCQ were examined using partial correlations controlling for the effects of age, gender and IQ.

Parts 2 to 4 – Subject group divided by SIS (part 2), SCQ (part 3) and both (part 4)

Group differences in the clinical symptoms derived from the CIS were analysed using chi^2 with Fishers exact test used when more than 20% of the cells contained less than 5 individuals. When the overall chi^2 was significant, examination of the standardised residuals was used to determine which cells produced the significant result.

Group differences in the structural measures were analysed using multiple ANCOVAs with the structure in question as the variable, group and gender as fixed factors, pedigree as a random factor and age as a covariate. When a main effect of at least trend level significance ($p<0.1$) was found post hoc between-group comparisons were carried out. The analyses were repeated, first with the addition of height as a covariate and then, for the callosal measures, with the addition of whole brain volume to the analysis to determine if the size differences identified were proportionate to an increase in the overall brain volume. In addition the appropriate prefrontal lobe volume was added as a covariate to the GI analyses to determine if differences in the GI reflected prefrontal volume differences or other factors.

Exploratory analyses were carried out separately to look for associations between the structural measures and symptoms. Only the subject groups which showed differences from the controls on both symptoms and brain structure were included and only those symptoms and brain structures which were actually abnormal were analysed. For those measures which were normally distributed ANCOVAs were used with the structure as the dependent variable, symptom and gender as fixed factors and covarying for age.

Standardised residual plots were checked for each ANCOVA. For those which were not normally distributed a Mann-Whitney test was used. Note that the Mann-Whitney test does not allow for covariates.

Chapter 6

Results

6.1 Part 1 – Whole Group

Demographic and Clinical Features of subjects and controls

The demographic characteristics, IQ and mean scores on the SIS, CBCL and SCQ of the subjects in special education and of the controls are shown in Table 6.1. The results for the CIS are given in Table 6.2. In general the subjects score more highly than the controls on measures of psychopathology although the controls do have significantly higher rates of phobic anxiety. Note that data for the controls are provided for reference only to allow the reader to gain some sense of the overall characteristics of the subject group; no investigation of the relationship between brain structure and symptoms are included here as the heterogeneity of the subject group makes interpretation difficult at this stage.

	Subjects	**Unimpaired Controls**
N	138	55
Gender (M:F)	85:53	28:27
Age	15.8 (1.6)	16.9 (2.1)
Height	166.6 (8.6)	167.6 (8.8)
IQ	72.7 (16.7)	100.9 (15.4)
SIS	30.9 (10.7)	18.7 (5.7)
CBCL	79.0 (34.8)	25.2 (21.9)
SCQ	14.2 (6.5)	5.5 (2.1)

Table 6.1

Demographic characteristics, IQ and mean SIS, CBCL and SCQ scores of subjects and controls

	Subjects	Controls	P value
Somatic Symptoms			
Absent/Mild	86.1	90.7	0.39
Morbid	13.9	9.3	
Bodily functions			
Absent/Mild	94.9	94.4	>0.99
Morbid	5.1	5.6	
Fatigue			
Absent/Mild	86.1	90.7	0.39
Morbid	13.9	9.3	
Sleep disturbance			
Absent/Mild	90.5	92.6	0.78
Morbid	9.5	7.4	
Irritability			
Absent/Mild	80.3	94.4	0.02
Morbid	19.7	5.6	
Lack of concentration			
Absent/Mild	83.2	98.1	0.003
Morbid	16.8	1.9	
Depression			
Absent/Mild	81.8	94.4	0.03
Morbid	18.2	5.6	
Depressive thoughts			
Absent/Mild	86.9	96.3	0.06
Morbid	13.1	3.7	
Elation			
Absent/Mild	97.1	100	0.58
Morbid	2.9	0	
Anxiety			
Absent/Mild	79.6	83.3	0.55
Morbid	20.4	16.7	
Phobias			
Absent/Mild	90.5	77.8	0.02
Morbid	9.5	22.2	
Obsessions/Compulsions			
Absent/Mild	78.8	96.3	0.003
Morbid	21.2	3.7	
Depersonalisation			
Absent/Mild	94.2	94.4	>0.99
Morbid	5.8	5.6	
Slowness			
Absent/Mild	88.2	100	0.007
Morbid	11.8	0	
Suspicion			
Absent/Mild	97.1	100	0.58
Morbid	2.9	0	

Histrionic			
Absent/Mild	100	100	-
Morbid	0	0	
Observed depression			
Absent/Mild	94.1	100	0.11
Morbid	5.9	0	
Observed agitation			
Absent/Mild	93.4	100	0.06
Morbid	6.6	0	
Observed elation			
Absent/Mild	100	100	-
Morbid	0	0	
Flattening of affect			
Absent/Mild	95.6	100	0.19
Morbid	4.4	0	
Delusions			
Absent/Mild	90.4	96.3	0.24
Morbid	9.6	3.7	
Passivity phenomena			
Absent/Mild	98.5	100	>0.99
Morbid	1.5	0	
Hallucinations			
Absent/Mild	82.4	98.1	0.004
Morbid	17.6	1.9	
Incongruity of affect			
Absent/Mild	97.8	100	0.56
Morbid	2.2	0	
Incoherence of speech			
Absent/Mild	97.8	100	0.56
Morbid	2.2	0	
Poverty of Speech			
Absent/Mild	85.3	100	0.001
Morbid	14.7	0	

Table 6.2

Frequency of symptoms and manifest abnormalities as measured by the CIS in subjects and controls

Results are given as percentages of total group

Statistic is chi^2 or Fishers exact test when over 20% of cells contain fewer than 5 individuals

Continuous relationships between SIS, SCQ and neuroanatomical variables within the participants receiving special educational assistance

SIS and SCQ

There was no evidence of a correlation between the SIS and the SCQ ($r=0.04$, $p=0.62$).

SIS and brain structure

There were no significant correlations between any region and total SIS score after covarying for age and gender, although there was a trend towards a weak positive correlation between SIS score and brain volume ($r=0.17$, $p=0.06$). The addition of IQ as a covariate made no difference to the results.

SCQ and brain structure

Significant correlations were found between total SCQ and the size of the rostral body and posterior midbody of the corpus callosum after covarying for age and gender ($r=0.19$, $p=0.04$ and $r=0.21$, $p=0.02$ respectively). There was a trend towards a positive correlation between the rostrum size and SCQ ($r=0.17$, $p=0.06$). Again, the addition of IQ as a covariate made no difference to the results.

6.2 Part 2 - Schizotypy

Description of Groups

The demographic characteristics, mean IQ and mean scores on the SIS, CBCL and SCQ of the three groups are shown in Table 6.3. As would be expected the unimpaired controls had a significantly higher mean IQ and lower SIS, CBCL and SCQ scores than the other groups. Importantly there were no differences between the SIS+ subjects and the educational controls on IQ, SCQ or CBCL. The unimpaired controls were significantly older than the other two groups ($F=7.7$, $p=0.01$) and had a higher proportion of females (although this did not reach statistical significance - $chi^2=2.69$, $p=0.26$).

	SIS+ subjects	**Educational Controls**	**Unimpaired Controls**
N	72	66	55
Gender (M:F)	47:25	38:28	28:27
Age	15.8 (1.7)	15.8 (1.5)	16.9 (1.8)
Height	167.3 (8.1)	165.9 (9.1)	167.6 (8.9)
IQ	74.4 (17.7)	70.9 (15.5)	100.9 (15.4)
SIS	37.9 (7.7)	21.5 (5.9)	18.7 (5.7)
CBCL	78.3 (33.3)	79.8 (36.6)	25.2 (21.9)
SCQ	14.0 (6.9)	14.3 (6.0)	5.5 (2.1)

Table 6.3

Demographic characteristics and mean IQ, SIS, CBCL and SCQ scores of participants by group

Results are shown as mean (SD)

Clinical Features

The CIS symptom categories for each of the groups are summarised in Table 6.4. Significant differences were found for many of the symptoms with the SIS+ subjects experiencing the highest degree of psychopathology. Compared to the educational controls and the unimpaired controls the SIS+ group had a higher prevalence of morbid fatigue, irritability, depression, depressive thoughts, anxiety, obsessions and compulsions, slowness, suspiciousness, delusions and hallucinations. Differences which exist between the SIS+ subjects and the unimpaired controls but which are not seen between the SIS+ and the educational controls are likely to relate to IQ rather than schizotypal status – an example of this would be lack of concentration.

Neurostructural Measures

The results for the region-of-interest and gyrification index comparisons are summarised in Table 6.5. The mean values for each, adjusted for age, gender and pedigree are given, as are the main effects (F) and significance (p) of the ANCOVAs. The between group comparisons are given for those results where the main effect showed at least a trend towards significance (i.e. when $p<0.1$). Results for the between group comparisons are given in the final column with those which only showed trends towards significance given in brackets.

	SIS+ Subjects	Educational Controls	Unimpaired Controls	P value
Somatic symptoms				
Absent/Mild	87.3	84.8	90.7	0.63
Morbid	12.7	15.2	9.3	
Bodily functions				
Absent/Mild	94.4	95.5	94.4	>0.99
Morbid	5.6	4.5	5.6	
Fatigue				
Absent/Mild	78.9	93.9	90.7	0.02
Morbid	21.1	6.1	9.3	
Sleeplessness				
Absent/Mild	87.3	93.9	92.6	0.36
Morbid	12.7	6.1	7.4	
Irritability				
Absent/Mild	73.2	87.9	94.4	0.003
Morbid	26.8	12.1	5.6	
Lack of concentration				
Absent/Mild	81.7	84.8	98.1	0.02
Morbid	18.3	15.2	1.9	
Depression				
Absent/Mild	76.1	87.9	94.4	0.01
Morbid	23.9	12.1	5.6	
Depressive thoughts				
Absent/Mild	81.7	92.4	96.3	0.02
Morbid	18.3	7.6	3.7	
Elation				
Absent/Mild	98.6	95.5	100	0.32
Morbid	1.4	4.5	0	
Anxiety				
Absent/Mild	71.8	87.9	83.3	0.05
Morbid	28.2	12.1	16.7	
Phobias				
Absent/Mild	88.7	92.4	77.8	0.05
Morbid	11.3	7.6	22.2	
Obsessions/Compulsions				
Absent/Mild	71.8	86.4	96.3	0.001
Morbid	28.2	13.6	3.7	
Depersonalisation				
Absent/Mild	93.0	95.5	94.4	0.92
Morbid	7.0	4.5	5.6	
Slow				
Absent/Mild	81.4	95.5	100	<0.001
Morbid	18.6	4.5	0	

Suspicion				
Absent/Mild	94.3	100	100	0.04
Morbid	5.7	0	0	
Histrionic				
Absent/Mild	100	100	100	-
Morbid	0	0	0	
Observed depression				
Absent/Mild	91.4	97.0	100	0.06
Morbid	8.6	3.0	0	
Observed agitation				
Absent/Mild	90.0	97.0	100	0.03
Morbid	10.0	3.0	0	
Observed elation				
Absent/Mild	100	100	100	-
Morbid	0	0	0	
Flattening of affect				
Absent/Mild	95.7	95.5	100	0.29
Morbid	4.3	4.5	0	
Delusions				
Absent/Mild	82.9	98.5	96.3	0.001
Morbid	17.1	1.5	3.7	
Passivity phenomena				
Absent/Mild	97.1	100	100	0.33
Morbid	2.9	0	0	
Hallucinations				
Absent/Mild	71.4	93.9	98.1	<0.001
Morbid	28.6	6.1	1.9	
Incongruity of affect				
Absent/Mild	97.1	98.5	100	0.78
Morbid	2.9	1.5	0	
Incoherence of speech				
Absent/Mild	95.7	100	100	0.11
Morbid	1.3	0	0	
Poverty of Speech				
Absent/Mild	82.9	87.9	100	0.008
Morbid	17.1	12.1	0	

Table 6.4

CIS scores for the SIS+, educational control and unimpaired control groups

Results are given as percentages of total group

Statistic is chi^2 or Fishers exact test when over 20% of cells contain fewer than 5 individuals

	SIS+ (1)	Educational Controls (2)	Unimpaired Controls (3)	F	P	Between group tests
Whole Brain	1359.4 (17.9)	1291.5 (20.3)	1355.6 (20.2)	2.52	0.09	1>2*
Prefrontal Lobe						
Total	138.8 (4.2)	124.9 (4.4)	128.8 (4.5)	1.97	0.15	-
Right	72.1 (2.2)	64.0 (2.3)	65.8 (2.3)	2.56	0.09	1>2,(3)**
-GM	50.1 (1.5)	45.3 (1.5)	46.0 (1.6)	2.15	0.13	-
-WM	22.0 (0.8)	18.7 (0.8)	18.7 (0.8)	3.01	0.06	1>2,(3)†
-GI	2.36 (0.02)	2.35 (0.02)	2.34 (0.02)	0.20	0.82	-
Left	66.7 (2.1)	60.9 (2.2)	63.0 (2.2)	1.34	0.27	-
-GM	47.4 (1.4)	43.9 (1.5)	44.8 (1.6)	1.07	0.35	-
-WM	19.3 (0.7)	17.0 (0.7)	18.2 (0.7)	1.70	0.20	-
-GI	2.34 (0.02)	2.35 (0.02)	2.35 (0.02)	0.06	0.94	-
Corpus Callosum						
Total	404.0 (13.7)	424.1 (15.1)	435.8 (14.7)	1.08	0.35	-
Rostrum	10.9 (1.4)	16.9 (1.5)	13.5 (1.5)	2.91	0.07	1<2††
Genu	94.0 (5.5)	85.2 (6.1)	94.2 (5.9)	0.52	0.60	-
R. Body	56.5 (2.7)	59.0 (2.9)	56.8 (2.8)	0.16	0.85	-
A. Midbody	47.9 (1.9)	47.9 (2.1)	51.5 (2.1)	0.93	0.40	-
P. Midbody	46.3 (1.6)	47.8 (1.8)	50.4 (1.7)	1.3	0.27	-
Isthmus	30.5 (1.9)	35.3 (2.1)	38.0 (2.0)	3.2	0.05	1<3‡
Splenium	117.9 (4.9)	131.9 (5.4)	131.5 (5.2)	1.85	0.17	-

Table 6.5

Adjusted means for the regions of interest and gyrification index

Results are given as mean (SE).

Units are mm3 for whole brain and prefrontal volume and mm2 for corpus callosum and sub-regions.

Between group comparisons in brackets are trend level significance (<0.1)

*p=0.05; **p=0.04, (0.08); †p=0.02, (0.09); ††p=0.02; ‡p=0.02

The SIS+ subjects had a larger mean brain volume and also showed enlargement of the right prefrontal lobe, particularly the white matter compared to both control groups, although this was only a trend versus the unimpaired controls. In addition the SIS+ group had a significantly smaller callosal rostrum than the educational controls and a smaller isthmus of the corpus callosum than the unimpaired controls with similar but non-significant differences seen for the other control group in each case. There were no significant differences observed for the other callosal regions or for the prefrontal gyrification index on either side.

The addition of whole brain volume as a covariate made the isthmus result significant against both groups of controls but otherwise had no significant effect on any of the callosal results. Similarly the addition of height as a covariate did not affect the results.

Relationship between abnormal neurostructural measures and symptoms in SIS+ group

Depressive thoughts were associated with a larger isthmus ($F=3.92$, $p=0.05$) and there was a trend for anxiety to be associated with enlarged right prefrontal lobes ($F=3.08$, $p=0.08$). Although the numbers were very small (4 vs. 59) necessitating the use of non-parametric statistics, people with morbid levels of suspiciousness had a significantly reduced size of the isthmus of the corpus callosum. ($Z=2.28$, $p=0.02$). There were no other associations between symptoms and the abnormal brain structural measures.

6.3 Part 3 – Pervasive Developmental Disorders

The demographic characteristics, mean IQ, SCQ, SIS and CBCL scores of the four groups defined by the SCQ cut-offs are shown in Table 6.6. The controls had a significantly higher mean IQ than each of the other three groups and were significantly older than the autism and educational control groups. There were no significant differences between the autism, PDD-NOS and educational control groups with respect to SIS score.

	Autism	**PDD-NOS**	**Educational Controls**	**Controls**
N	23	35	77	55
Gender (M:F)	18:5	22:13	42:35	28:27
Age	15.7 (1.6)	16.3 (1.8)	15.7 (1.5)	16.9 (1.8)
Height	167.9 (11.2)	167.1 (9.5)	165.8 (7.1)	167.6 (8.9)
IQ	69.4 (17.2)	73.7 (19.3)	73.7 (15.5)	100.9 (15.4)
SCQ	24.9 (2.6)	17.4 (1.7)	9.5 (3.1)	5.5 (2.1)
SIS	29.2 (8.9)	31.6 (12.4)	30.0 (10.6)	18.7 (5.7)
CBCL	98.2 (38.2)	93.7 (29.3)	66.0 (30.6)	25.2 (21.9)

Table 6.6

Demographic characteristics and mean IQ, SCQ, SIS and CBCL scores of the four groups

Clinical Features

The CIS scores for each of the four groups are shown in Table 6.7. Significant differences were seen between the groups for sleep disturbance, concentration, depression, obsessions and compulsions, slowness, observed depression, hallucinations and poverty of speech. The autism group showed increased rates of slowness and

poverty of speech compared to any of the other groups and both the autism and PDD-NOS groups had poor concentration. For the remainder of the symptoms it was the PDD-NOS group who were particularly morbid, especially with respect to hallucinations.

Neurostructural Measures

The autism group showed significant reductions in right prefrontal GI compared to each of the other three groups. There were no significant differences in other prefrontal lobe measures. The genu of the corpus callosum was significantly smaller in the autism and the PDD-NOS groups relative to the educational controls and there was a trend towards a reduction for the autism group when compared to the unimpaired controls. The rostrum and the rostral body of the corpus callosum were larger in the autism and the PDD-NOS groups relative to the educational controls although this was only a trend for the rostrum in the PDD-NOS group and the rostral body in the autism group.

When whole brain volume was added as a covariate to the callosal measures, the main effect for the rostral body result became significant. The addition of height as a covariate did not affect the results significantly.

Relationship between abnormal neurostructural measures and symptoms in autism and PDD-NOS

There was a trend for poverty of speech to be associated with an enlarged rostral body of the corpus callosum in the autism group ($F=3.42$, $p=0.08$). No other symptom-structure associations were seen.

	Autism	PDD-NOS	Educational Controls	Unimpaired Controls	P Value
Somatic symptoms					
Absent/Mild	87.0	77.1	89.5	90.7	0.28
Morbid	13.0	22.9	10.5	9.3	
Bodily functions					
Absent/Mild	100	91.4	94.7	94.4	0.65
Morbid	0	8.6	5.3	5.6	
Fatigue					
Absent/Mild	87.0	74.3	90.8	90.7	0.10
Morbid	13.0	25.7	9.2	9.3	
Sleep disturbance					
Absent/Mild	100	80.0	93.4	92.6	0.05
Morbid	0	20.0	6.6	7.4	
Irritability					
Absent/Mild	87.0	77.1	80.3	94.4	0.08
Morbid	13.0	22.9	19.7	5.6	
Lack of Concentration					
Absent/Mild	78.3	77.1	86.8	98.1	0.005
Morbid	21.7	22.9	13.2	1.9	
Depression					
Absent/Mild	91.3	74.3	84.2	94.4	0.05
Morbid	8.7	25.7	15.8	5.6	
Depressive thoughts					
Absent/Mild	91.3	82.9	88.2	96.3	0.17
Morbid	8.7	17.1	11.8	3.7	
Elation					
Absent/Mild	100	100	96.1	100	0.45
Morbid	0	0	3.9	0	
Anxiety					
Absent/Mild	91.3	82.9	75.0	83.3	0.31
Morbid	8.7	17.1	25.0	16.7	
Phobias					
Absent/Mild	95.7	88.6	90.8	77.8	0.11
Morbid	4.3	11.4	9.2	22.2	
Obsessions/Compulsions					
Absent/Mild	78.3	68.6	84.2	96.3	0.005
Morbid	21.7	31.4	15.8	3.7	
Depersonalisation					
Absent/Mild	95.7	94.3	93.4	94.4	>0.99
Morbid	4.3	5.7	6.6	5.6	
Slowness					
Absent/Mild	77.3	91.4	89.5	100	0.004
Morbid	22.7	8.6	10.5	0	

Suspicion					
Absent/Mild	95.5	94.3	98.7	100	0.18
Morbid	4.5	5.7	1.3	0	
Histrionic					
Absent/Mild	100	100	100	100	-
Morbid	0	0	0	0	
Observed depression					
Absent/Mild	95.5	86.6	97.4	100	0.03
Morbid	4.5	11.4	2.6	0	
Observed agitation					
Absent/Mild	95.5	91.4	93.4	100	0.12
Morbid	4.5	8.6	6.6	0	
Observed elation					
Absent/Mild	100	100	100	100	-
Morbid	0	0	0	0	
Flattening of affect					
Absent/Mild	90.9	94.3	97.4	100	0.09
Morbid	9.1	5.7	2.6	0	
Delusions					
Absent/Mild	95.5	82.9	92.1	96.3	0.17
Morbid	4.5	17.1	7.9	3.7	
Passivity phenomena					
Absent/Mild	100	97.1	98.7	100	0.60
Morbid	0	2.9	1.3	0	
Hallucinations					
Absent/Mild	95.5	68.6	84.2	98.1	<0.001
Morbid	4.5	31.4	15.8	1.9	
Incongruity of affect					
Absent/Mild	90.9	100	98.7	100	0.06
Morbid	9.1	0	1.3	0	
Incoherence of speech					
Absent/Mild	95.5	97.1	98.7	100	0.32
Morbid	4.5	2.9	1.3	0	
Poverty of speech					
Absent/Mild	68.2	88.6	88.2	100	<0.001
Morbid	31.8	11.4	11.8	0	

Table 6.7

CIS scores for the autism, PDD-NOS, educational control and unimpaired control groups

Results are given as percentages of total group

Statistic is chi^2 or Fishers exact test when over 20% of cells contain fewer than 5 individuals

	Autism (1)	PDD-NOS (2)	Educational Controls (3)	Unimpaired Controls (4)	F	P	Between group tests
Whole Brain	1297.1 (46.6)	1287.5 (37.7)	1352.8 (19.4)	1352.3 (21.1)	1.09	0.37	-
Prefrontal Lobe							
Total	138.4 (11.0)	121.2 (8.2)	134.8 (4.3)	129.4 (4.7)	0.80	0.50	-
Right	72.3 (5.8)	62.0 (4.3)	69.5 (2.3)	66.2 (2.5)	1.02	0.39	-
-GM	50.2 (3.8)	43.7 (2.9)	48.7 (1.5)	46.2 (1.6)	1.06	0.38	-
-WM	22.1 (2.1)	18.3 (1.6)	18.3 (1.6)	19.9 (0.9)	0.82	0.49	-
-GI	2.23 (0.04)	2.38 (0.03)	2.39 (0.02)	2.34 (0.02)	3.02	0.04	1<2,3,4*
Left	66.1 (5.4)	59.2 (4.0)	65.3 (2.2)	63.2 (2.3)	0.58	0.63	-
-GM	47.2 (3.8)	42.4 (2.8)	46.6 (1.5)	45.0 (1.6)	0.59	0.62	-
-WM	18.9 (1.8)	16.8 (1.4)	18.7 (0.7)	18.2 (0.8)	0.45	0.72	-
-GI	2.27 (0.05)	2.34 (0.04)	2.35 (0.02)	2.35 (0.02)	0.91	0.45	-
Corpus Callosum							
Total	384.2 (32.3)	409.4 (26.7)	423.0 (14.5)	433.6 (14.9)	0.83	0.49	-
Rostrum	18.8 (3.2)	17.0 (2.6)	10.4 (1.4)	13.8 (1.5)	2.24	0.10	1,(2)>3**
Genu	67.8 (12.0)	75.1 (10.0)	103.1 (5.4)	92.7 (5.6)	2.89	0.05	1,2<3†; (1<4)††
R. Body	65.3 (5.8)	65.4 (4.8)	51.6 (2.6)	57.1 (2.7)	2.28	0.09	(1),2>3‡
A. Midbody	50.2 (4.6)	45.1 (3.8)	48.3 (2.1)	51.6 (2.1)	0.84	0.48	-
P. Midbody	45.7 (3.1)	45.7 (3.1)	47.9 (1.7)	50.2 (1.8)	0.96	0.42	-
Isthmus	28.8 (4.4)	29.7 (3.7)	34.9 (2.0)	37.7 (2.0)	2.09	0.12	-
Splenium	107.9 (11.6)	131.4 (9.5)	126.8 (5.2)	130.5 (5.3)	1.15	0.34	-

Table 6.8

Adjusted means for the regions of interest and gyrification index

Results are given as mean (SE) and units are mm3 for whole brain and prefrontal volume and mm^2 for corpus callosum and sub-regions.

Between group comparisons in brackets are trend level significance (<0.1)

*p=0.02, <0.006, 0.03; **p=0.04, 0.06; ††p=0.02, 0.04; ††p=0.06; ‡p=0.07, 0.04

6.4 Part 4 - Comorbidity of Schizotypy and Pervasive Developmental Disorders

Characteristics of Subject Groups

The demographic characteristics along with the mean IQ, SIS, SCQ and CBCL scores for each of the groups are given in Table 6.9. There were significant differences in gender and age between the groups but not height. The unimpaired controls had a higher mean IQ but there were no significant IQ differences between the other groups. Clearly differences will exist in SIS and SCQ score between the groups but it is interesting to note that the comorbid PDD group had a significantly higher SIS score than any of the other groups including the comorbid autism group and the SIS+ group.

	Comorbid Autism	***Comorbid PDD-NOS***	***SIS+***	***Autism***	***PDD-NOS***	***Educational Controls***	***Unimpaired Controls***
N	13	17	42	10	18	35	55
M:F	11:2	12:5	24:18	7:3	10:8	18:17	28:27
Age	15.8 (1.9)	16.1 (1.7)	15.7 (1.7)	15.6 (1.2)	16.4 (2.0)	15.7 (1.2)	16.9 (2.1)
Height	167.9 (9.1)	169.3 (8.8)	166.4 (7.6)	168.0 (13.9)	165.1 (9.9)	165.1 (6.5)	167.6 (8.9)
IQ	70.7 (20.3)	76.5 (19.6)	74.8 (16.3)	67.6 (12.8)	71.1 (19.3)	72.4 (14.7)	100.9 (15.4)
SIS	35.4 (4.8)	41.2 (9.1)	37.4 (7.6)	21.2 (6.1)	22.6 (7.0)	21.0 (5.6)	18.7 (5.7)
CBCL	95.3 (26.7)	105.4 (28.7)	62.1 (26.9)	102.0 (50.8)	82.7 (25.9)	70.7 (34.3)	25.2 (21.9)
SCQ	25.4 (3.2)	17.5 (1.6)	9.2 (2.9)	24.2 (1.7)	17.3 (1.8)	9.9 (3.3)	5.5 (2.1)

Table 6.9

Demographic characteristics, mean IQ, SIS, CBCL and SCQ scores of the subject and control groups
Results are given as mean (standard deviation)

Clinical Features

The CIS symptom categories for each group are shown in Table 6.10. The comorbid PDD-NOS was the most strikingly morbid group in terms of not only general symptoms such as fatigue and irritability but also more specific symptoms including depressive symptoms, obsessive-compulsive behaviour, delusions and hallucinations. The SIS+ group were more anxious than any of the other groups and showed increased rates of delusions and hallucinations similar to the comorbid PDD-NOS group although they did not have the same degree of other symptomatology. In contrast the PDD-NOS group were not particularly symptomatic as measured by the CIS. Both the autism and the comorbid autism groups showed morbid levels of poverty of speech and the comorbid autism group also scored highly for slowness. Neither were particularly morbid on other measures including psychotic symptoms when compared to the other groups.

Neurostructural data

The results of the ANCOVAs for the regions of interest and the GI are shown in Table 6.11. The PDD-NOS group showed a reduction in both the grey and white matter in the right prefrontal lobe relative to almost all the other groups including the comorbid PDD-NOS group. Similar to the findings in Part 2 the SIS+ group showed enlargements in the right prefrontal lobe and reductions in the size of the callosal rostrum relative to the control groups. The autism group showed a trend towards increased right prefrontal grey matter and a significantly increased rostrum of the corpus callosum relative to the control groups.

Neurostructural Measures with respect to symptoms

Morbid levels of anxiety in the SIS+ group were associated with increased prefrontal lobe measures particularly on the right side (total prefrontal lobe – $F=6.89$, $p=0.01$; right prefrontal lobe – $F=7.12$, $p=0.01$, right prefrontal GM – $F= 6.40$, $p=0.02$; right prefrontal WM – $F=6.62$, $p=0.02$). No other structure-symptom relationships were seen in those groups that had both morbid symptomatology and brain structural differences relative to controls.

	Comorbid Autism	Comorbid PDD-NOS	SIS+	Autism	PDD-NOS	Educational Controls	Unimpaired Controls	P Value
Somatic symptoms								
Absent/Mild	84.6	76.5	92.7	90.0	77.8	85.7	90.7	0.54
Morbid	13.4	23.5	7.3	10.0	22.2	14.3	9.3	
Bodily functions								
Absent/Mild	100.0	88.2	95.1	100.0	94.4	94.3	94.4	0.93
Morbid	0	11.8	4.9	0	5.6	5.7	5.6	
Fatigue								
Absent/Mild	76.9	58.8	87.8	100.0	88.9	94.3	90.7	0.02
Morbid	23.1	41.2	12.2	0	11.1	5.7	5.3	
Sleep disturbance								
Absent/Mild	100.0	64.7	92.7	100.0	94.4	94.3	92.6	0.04
Morbid	0	35.3	7.3	0	5.6	5.7	7.4	
Irritability								
Absent/Mild	76.9	58.8	78.0	100.0	94.4	82.9	94.4	0.007
Morbid	23.1	41.2	22.0	0	5.6	17.1	5.6	
Lack Concentration								
Absent/Mild	76.9	64.7	90.2	80.0	88.9	82.9	98.1	0.004
Morbid	23.1	35.3	9.8	20.0	11.1	17.1	1.9	
Depression								
Absent/Mild	84.6	58.8	80.5	100.0	88.9	88.6	94.4	0.02
Morbid	15.4	41.2	19.5	0	11.1	11.4	5.6	
Depressive thoughts								
Absent/Mild	84.6	70.6	85.4	100.0	94.4	91.4	96.3	0.06
Morbid	15.4	29.4	14.6	0	5.6	8.6	3.7	
Elation								
Absent/Mild	100.0	100.0	97.6	100.0	100.0	94.3	100.0	0.48
Morbid	0	0	2.4	0	0	5.7	0	

Anxiety								
Absent/Mild	84.6	82.4	63.4	100.0	83.3	88.6	83.3	0.05
Morbid	15.4	17.6	36.6	0	16.7	11.4	16.7	
Phobias								
Absent/Mild	92.3	82.4	90.2	100.0	94.4	91.4	77.8	0.32
Morbid	7.7	17.6	9.8	0	5.6	8.6	22.2	
Obsess./Compuls.								
Absent/Mild	76.9	47.1	80.5	80.0	88.9	88.6	96.3	<0.001
Morbid	23.1	52.9	19.5	20.0	11.1	11.4	3.7	
Depersonalisation								
Absent/Mild	92.3	88.2	95.1	100.0	100.0	91.4	94.4	0.78
Morbid	7.7	11.8	4.9	0	0	8.6	5.6	
Slowness								
Absent/Mild	66.7	88.2	82.9	90.0	94.4	97.1	100.0	0.001
Morbid	33.3	11.8	17.1	10.0	5.6	2.9	0	
Suspicion								
Absent/Mild	91.7	88.2	97.6	100.0	100.0	100.0	100.0	0.04
Morbid	8.3	11.8	2.4	0	0	0	0	
Histrionic								
Absent/Mild	100.0	100.0	100.0	100.0	100.0	100.0	100.0	-
Morbid	0	0	0	0	0	0	0	
Obs. depression								
Absent/Mild	91.7	82.4	95.1	100.0	94.4	100.0	100.0	0.02
Morbid	8.3	17.6	4.9	0	5.6	0	0	
Anxiety/agitation								
Absent/Mild	100.0	82.4	90.2	90.0	100.0	97.1	100.0	0.02
Morbid	0	17.6	9.8	10.0	0	2.9	0	
Obs. Elation								
Absent/Mild	100.0	100.0	100.0	100.0	100.0	100.0	100.0	-
Morbid	0	0	0	0	0	0	0	

Flattened affect	91.7	94.1	97.6	90.0	94.4	97.1	100.0	0.15
Absent/Mild	8.3	5.9	2.4	10.0	5.6	2.9	0	
Morbid								
Delusions	91.7	64.7	87.8	100.0	100.0	97.1	96.3	0.005
Absent/Mild	8.3	35.3	12.2	0	0	2.9	3.7	
Morbid								
Passivity phenom	100.0	94.1	97.6	100.0	100.0	100.0	100.0	0.40
Absent/Mild	0	5.9	2.4	0	0	0	0	
Morbid								
Hallucinations	91.7	47.1	75.6	100.0	88.9	94.3	98.1	<0.001
Absent/Mild	8.3	52.9	24.4	0	11.1	5.7	1.9	
Morbid								
Incongruity of affect	91.7	100.0	97.6	90.0	100.0	100.0	100.0	0.05
Absent/Mild	8.3	0	2.4	10.0	0	0	0	
Morbid								
Speech incoherence	91.7	94.1	97.6	100.0	100.0	100.0	100.0	0.16
Absent/Mild	8.3	5.9	2.4	0	0	0	0	
Morbid								
Poverty of speech	66.7	82.4	87.8	70.0	94.4	88.6	100.0	0.001
Absent/Mild	33.3	17.6	12.2	30.0	5.6	11.4	0	
Morbid								

Table 6.10

CIS symptom categories for the 7 groups. Results are given as percentages of total group.

Statistic is chi^2 or Fishers exact test when over 20% of cells contain fewer than 5 individuals

	Comorbid Autism (1)	Comorbid PDD-NOS (2)	SIS+ (3)	Autism (4)	PDD-NOS (5)	Educational Controls (6)	Unimpaired Controls (7)	F	P	Between group tests
Whole Brain	1279.2 (58.6)	1367.9 (61.2)	1382.6 (27.5)	1314.0 (57.7)	1216.7 (52.2)	1309.1 (29.6)	1351.1 (20.6)	1.68	0.15	-
Prefrontal Lobe										
Total	129.6 (12.1)	143.1 (12.7)	142.0 (6.0)	149.9 (13.7)	102.8 (10.6)	125.7 (6.0)	128.4 (4.3)	2.24	0.06	5<2,3,4,(6),7*; (3>6,7)**
Right	67.8 (6.2)	75.0 (6.5)	73.4 (3.1)	78.1 (7.0)	51.2 (5.4)	64.4 (3.1)	65.6 (2.2)	2.79	0.03	5<(1),2,3,4,6,7†; (3>6,7)††; (4>7)†††
-GM	46.7 (4.2)	51.8 (4.3)	51.2 (2.0)	54.7 (4.7)	36.9 (3.6)	45.5 (2.1)	45.9 (1.5)	2.67	0.03	5<2,3,4,(6),7‡; 3>6,(7)‡‡; (4>6,7)‡‡‡
-WM	21.1 (2.3)	23.2 (2.4)	22.2 (1.1)	23.4 (2.6)	14.3 (2.0)	18.9 (1.1)	19.8 (0.8)	2.51	0.04	5<1,2,3,4,(6),7$^{\Omega}$; (3>6)$^{\Omega\Omega}$
-GI	2.21 (0.05)	2.44 (0.06)	2.39 (0.03)	2.26 (0.06)	2.33 (0.05)	2.38 (0.03)	2.33 (0.02)	1.89	0.11	-
Left	61.8 (6.1)	68.1 (6.4)	68.6 (3.0)	71.8 (6.9)	51.6 (5.4)	61.2 (3.0)	62.8 (2.2)	1.64	0.17	-
-GM	44.0 (4.3)	48.5 (4.5)	48.7 (2.1)	51.5 (4.8)	37.3 (3.8)	44.1 (2.1)	44.7 (1.5)	1.54	0.20	-
-WM	17.8 (2.1)	19.6 (2.2)	19.9 (1.0)	20.2 (2.4)	14.3 (1.9)	17.2 (1.1)	18.1 (0.75)	1.44	0.23	-
-GI	2.24 (0.06)	2.34 (0.07)	2.37 (0.03)	2.31 (0.07)	2.35 (0.06)	2.37 (0.03)	2.34 (0.02)	0.52	0.79	-
C. Callosum										
Total	369.0 (41.0)	441.0 (48.7)	403.7 (21.7)	393.9 (45.8)	393.5 (37.2)	443.5 (23.6)	428.8 (15.6)	0.74	0.63	-
Rostrum	15.6 (3.9)	13.4 (4.6)	8.5 (2.1)	23.1 (4.3)	19.8 (3.5)	13.2 (2.2)	13.8 (1.5)	2.11	0.07	3<4,5,7•; 4>3,(6),7••
Genu	65.3 (15.3)	94.5 (18.2)	103.7 (8.1)	68.3 (17.1)	62.3 (13.9)	100.5 (8.8)	91.1 (5.8)	1.71	0.14	-
R. Body	63.1 (7.5)	72.2 (8.9)	49.3 (4.0)	66.6 (8.3)	61.5 (6.8)	53.8 (4.3)	56.2 (2.8)	1.32	0.27	-
A. Midbody	46.5 (5.8)	52.6 (6.8)	47.4 (3.0)	53.6 (6.4)	40.3 (5.2)	48.8 (3.3)	50.8 (2.2)	0.85	0.54	-
P. Midbody	42.0 (4.8)	50.2 (5.7)	46.7 (2.5)	48.8 (5.4)	42.9 (4.4)	49.1 (2.8)	49.7 (1.8)	0.84	0.55	-
Isthmus	24.5 (5.6)	29.3 (6.6)	32.8 (3.0)	33.9 (6.2)	30.4 (5.1)	37.6 (3.2)	37.3 (2.1)	1.48	0.21	-
Splenium	112.1 (14.1)	128.8 (16.8)	115.2 (7.5)	99.6 (15.8)	136.4 (12.8)	140.5 (8.1)	129.8 (5.4)	1.47	0.21	-

Table 6.11

Adjusted means for the regions of interest and gyrification index

Results are given as mean (SE).

Units are mm3 for whole brain and prefrontal volume and mm2 for corpus callosum and sub-regions.

Between group comparisons in brackets are trend level significance (<0.1)

*p=0.03, 0.004, 0.02, 0.08, 0.04; **p=0.08, 0.09; †p=0.07, 0.01, 0.002, 0.007, 0.05, 0.02; ††p=0.06, 0.06; †††p=0.1; ‡p=0.02, 0.002, 0.008, 0.05, 0.04; ‡‡p=0.08, 0.05; ‡‡‡p=0.1, 0.08; Ωp=0.05, 0.01, 0.002, 0.01, 0.07, 0.02; ΩΩp=0.06; •p=0.006, 0.01, 0.05; ••p=0.07, 0.05

Chapter 7

Discussion

7.1 Schizotypy

Clinical Findings

It is clear from the findings on the CIS that the SIS cut-off does indeed identify a group with a high degree of schizotypal psychopathology. Particularly striking are the high rates of delusions and hallucinations in the SIS+ group (17.1% and 28.6% respectively). In contrast, these symptoms are much rarer in either of the control groups. All of the subjects were derived from a non-clinical population and although they did have scores within the range considered morbid on individual psychotic symptoms, none of the SIS+ group were considered to be suffering from an actual psychotic illness at the time of assessment. Observed slowness at interview is another symptom which was virtually absent in the control groups but is present to a morbid degree in a significant proportion of the SIS+ group (18.6%). A look at the raw CIS scores reveals that the majority of those rated as morbid were felt to be apathetic and lack spontaneity as opposed to suffering from true psychomotor retardation. It is likely that the morbid levels of slowness represent part of the negative dimension of schizotypy analogous to negative symptoms in schizophrenia.

High rates of obsessive-compulsive symptoms are also seen in the SIS+ group. Although not part of the diagnostic criteria obsessive symptoms are frequently seen in schizophrenia[213,214] and have been found to be associated with schizotypal personality traits.[215,216] In particular those obsessive thoughts which are highly unrealistic and considered by the individual to be threatening in their own right are thought to be

associated more with schizotypal personality disorder than obsessive-compulsive disorder (as opposed to those obsessions in which it is the consequences which are considered to be unpleasant).[217] Indeed from a clinical perspective it can be difficult to distinguish obsessional ideas from overvalued ideas and even delusions. Interest in the link between obsessive-compulsive disorder and schizophrenia has increased in recent years with some proposing that there exists a subtype of schizophrenia with prominent obsessive symptomatology.[218] Cortical regions which have been found to be abnormal in OCD centre around the orbitofrontal cortex and the frontostriatial network, both of which have also been implicated in schizophrenia.[219,220] In addition there are important reciprocal modulatory effects between the serotonin and dopamine systems[221] which are felt to be primarily responsible for OCD and schizophrenia respectively. Further evidence for this is seen in Tourette syndrome which is frequently comorbid with OCD and is treated with dopamine antagonists, leading some to suggest a dual role for serotonin and dopamine in the pathogenesis of OCD.[222]

Symptoms such as anxiety and depression were reported reasonably often in the control populations much as one would expect in normal adolescence, however were present to a greater degree in the schizotypal individuals. Again this is in agreement with the literature regarding comorbidity in schizophrenia and schizotypy.[223] Interestingly in the Edinburgh High Risk Study anxiety and depression were among the clinical variables which best predicted the later development of schizophrenia although it is not known whether such non-specific affective phenomena represent part of the causative mechanism or are secondary occurrences.[224]

Neurostructural Data

The reported results are consistent with hypotheses 1 and 4 but not 2 or 3. The SIS+ group showed an overall increase in brain volume and right prefrontal lobe volume (hypothesis 1), especially the right prefrontal white matter. No size differences were present when the remainder of the brain was considered, suggesting that the prefrontal enlargement is not part of a generalised enlargement of the entire brain. This fits with the observed reduction in the isthmus of the corpus callosum (hypothesis 4) which contains fibres originating in the temporal lobe, whereas the rostral size reductions suggest that within the prefrontal lobe itself the enlargements may not be uniform. Within the schizotypal subject group a smaller isthmus was associated with morbid levels of suspiciousness, while a larger one was associated with an increase in depressive thoughts. Morbid levels of anxiety were associated with enlarged right prefrontal white matter. Contrary to hypotheses 2 and 3 no significant differences in the size of the callosal genu or in prefrontal GI were seen between the groups.

In the largest structural MRI study of the prefrontal lobe in schizotypal personality disorder Suzuki et al found enlargements of the middle frontal gyrus and reductions in the right straight gyrus compared to controls.[54] The middle frontal gyrus makes up a large part of the lateral prefrontal cortex while the straight gyrus is a relatively small structure which lies on the ventromedial aspect of the prefrontal lobe abutting the orbitofrontal cortex. If a sufficient degree of enlargement is present in the middle frontal gyrus it is likely to obscure any reductions in the smaller straight gyrus when the total prefrontal volume is considered. The reduced size of the callosal rostrum reported in the current

study is consistent with this non-uniform pattern of prefrontal volumetric changes as the rostrum carries fibres which originate in the orbitofrontal cortex. A reduction in the posterior corpus callosum has also been previously reported in schizotypal personality disorder[60] and is consistent with findings of reduced temporal lobe volumes in schizotypal individuals.[57,61]

The lack of a significant difference in the size of the callosal genu (hypothesis 3) is contrary to the one previous study which has examined the size of the corpus callosum in schizotypal personality disorder.[60] A non-significant enlargement of this region was seen between the SIS+ group and the educational controls. It is possible that population differences account for the disagreement between the current study and previous work as the subjects considered here were younger. The corpus callsoum has been shown to continue development beyond adolescence[225] and it is possible that significant differences between the groups may emerge with time.

Contrary to hypothesis 2 no difference in prefrontal GI was seen between the groups. An increase in right prefrontal GI was reported in the EHRS in high risk subjects who later went on to develop schizophrenia compared to those who did not.[83] While a significant minority of the the SIS+ group considered here are expected to go on to develop schizophrenia the majority will not. The negative finding in this group suggests that an increase in right prefrontal GI is not a marker for schizotypy, but may instead be specifically related to the later development of schizophrenia.

Within the schizotypal sub-group those with a morbid level of anxiety possessed more right prefrontal white matter than those without. As mentioned above anxiety has been found to be an important predictor of the later development of schizophrenia.[224] Not all of the schizotypal subjects in this study will go on to develop schizophrenia, but it is probable that a significant minority will. Indeed this is one of the premises on which the ESC is based. The relationship between morbid anxiety and increased right prefrontal white matter suggests that those schizotypal individuals with more white matter have a worse prognosis than those without. There are two possible explanations for this. Firstly it is possible that an increase in right prefrontal white matter is in fact detrimental to the subjects and rather than protecting against schizophrenia it lies on the causative pathway. However, if this was the case one would expect to see increases in the prefrontal volume in schizophrenia, which is not the case,[226] and the evidence of compensatory prefrontal function in schizotypal personality disorder would not be seen. The second possibility is that the prefrontal white matter actually undergoes a relative expansion in the schizotypal group relative to the control groups to compensate for increasing levels of anxiety in the early stages of psychosis, which in turn may be the result of evolving temporal lobe deficits. One possible mechanism for this would be an increase in myelination in the prefrontal lobe. There is evidence that axonal activity promotes oligodendrocyte precursor cell proliferation[227] and that myelination in the prefrontal lobe continues into the third decade.[228] If parts of the frontal lobe are required to increase their function to compensate for structural abnormalities elsewhere this could lead to an increase in fibre myelination. This raises the possibility that in schizophrenia, in which oligodendrocyte abnormalities are known to occur,[229,230] this process has been unable to keep up with the

developing temporal lobe abnormalities and eventually fails altogether leading to the more severe clinical picture.

The reduction in the cross-sectional area of the isthmus is consistent with the idea that temporal lobe abnormalities are important in the pathogenesis of schizotypy. A morbid level of suspiciousness was associated with a small isthmus although the reliability of this result is limited by the small number of subjects who fell into this category. The temporal lobe is involved in several different aspects of social functioning, including facial affect recognition and theory of mind.[231,232] Deficits in either of these processes may lead to the misinterpretation of others motives and hence suspiciousness. Harder to explain is the finding that depressive thoughts are associated with a larger isthmus in the SIS+ group, particularly when depressed mood was not. Some studies have found an increased size of the posterior corpus callosum in depression, particularly in those with a family history of mood disorder and it has been suggested that this represents anomalous lateralisation and therefore emotional processing abilities.[233,234] It is unclear why the direction of the association is opposite to that of the group difference between the SIS+ subjects and the controls and the possibility of a Type 1 error should be considered.

In summary the results for the SIS+ group are in keeping with studies in schizotypal adults of normal IQ, with an enlargement of the prefrontal lobe, a reduction in the callosal rostrum which suggests these enlargements are not uniform throughout the prefrontal lobe and reductions in the posterior callosum consistent with temporal lobe structural abnormalities. These findings are supportive of the view that in schizotypy the

prefrontal lobe acts to buffer temporal lobe changes and hence prevent deterioration into schizophrenia. The relationship between anxiety and prefrontal lobe volume suggests that dynamic changes in this region may occur in response to the early development of psychosis although this hypothesis is only speculative and requires further investigation.

7.2 Pervasive Developmental Disorders

Clinical Findings

The most striking finding from the CIS data is the high prevalence of morbid psychopathology in the PDD-NOS group when compared to the autism or control groups. As hypothesised the autism group had a higher prevalence of symptoms which could be associated with autistic features including slowness, poverty of speech and affectual incongruity but they had noticeably low levels of other symptoms compared to the PDD-NOS group, and were generally not different from the educational controls in this respect. In itself this finding of relatively low rates of psychiatric symptoms which do not relate directly to autistic features is not surprising – after all the CIS is a measure of psychiatric symptomatology, not of social and communication difficulties. However, the high symptom prevalence in the PDD-NOS group, in the absence of such morbidity in the autism group, suggests that the PDD-NOS group is so affected for a reason other than their PDD. As discussed in chapter 1 PDD-NOS represents a more heterogeneous condition than autism and it is possible that within this group there are sub-groups, some of which may have high rates of psychopathology as they are not actually suffering from PDD but other conditions which have diagnostic overlaps. One possibility is schizotypy and this issue will be considered further in the section 7.3.

Neurostructural Features

The results of the region-of-interest analysis allowed only for the partial acceptance of hypothesis 4 in that the the autism and PDD-NOS groups both showed sub-regional

reduction in the corpus callosum, specifically a decrease in the size of the genu. However trends towards an increase in the rostrum and rostral body were also observed, with the increased rostral body being associated with poverty of speech in the autism group. Contrary to hypotheses 1 and 2 there were no differences seen in the whole brain volume or prefrontal volume for the autism or PDD groups and in direct contrast to hypothesis 3 the autism group had a significantly reduced right prefrontal GI compared to the control groups.

The genu reduction is consistent with previous research,[117] but the enlargements of the rostrum and rostral body are not. It should be borne in mind that the division of the genu from the anterior border of the rostral body is made using the same line which distinguishes it from the rostrum (see Figure 5.2). Movement of this line anteriorly will thus produce a reduction in the size of the genu and an increase in the size of the rostrum and rostral body, i.e. the pattern which is observed here. Such an anterior shift could be the result of shape differences in the corpus callosum, specifically a greater inner curve, rather than size differences per se.

If however the differences reported here represent true size differences in these sub-regions then the meaning must be considered in the context of what is known about PDD. While it is commonly accepted that larger structures equate to better function this relationship may not be so simple in PDD. The meta-analysis in chapter 3 found that both increases and decreases in the size of brain structures are associated with autism and indeed that this relationship may change over time. There is no evidence to support the

existence of compensatory-type hypotheses such as that discussed above for schizotypal disorder in autism thus it is possible that both the enlargements and the reductions of the callosal sub-regions reported here relate to functional deficits.

The rostrum carries fibres which connect the orbitofrontal cortices (OFC) in opposing hemispheres, thus the size difference in the rostrum may represent structural abnormalities in this brain region. The OFC is involved in impulse control and response prevention and, among other connections, forms part of the orbitofrontal-medial temporal circuit. This circuit is involved in social behaviour through the perception of social cues which is the role of medial temporal structures such as the amygdala, and the appropriate choice of behavioural response which is the role of the OFC.[235] Functional abnormalities in the orbitofrontal-medial temporal circuit have been reported in autism and are likely to relate to the social deficits which characterise the disorder.[236]

The rostral body of the corpus callosum primarily connects the premotor and supplementary motor regions of the frontal cortex in each hemisphere. Increasing interest has focused on the premotor region in autism due to the finding that neurones in this area are activated during both facial affect production and observation. It is hypothesised that the activation of these mirror neurones is due to the internal representation or mental imitation of another's expression as part of the process of correctly identifying the displayed affect.[237] A lack of activation of mirror neurones in the premotor cortex has been found in autistic individuals during observation and imitation of emotional facial expression suggesting that dysfunction in this system may

have a role to play in the deficits in emotional recognition seen in PDD.[238] Another reason for an enlargement of the rostral body in autism is suggested by the observed association with poverty of speech. Broca's area is a key region in the production of speech and lies immediately anterior to the premotor cortex in the dominant hemisphere. Alterations in the laterality in this region have been found to be associated with language impairment[138] and it is possible that this may manifest as an increase in interhemispheric fibres which pass through the rostral body. In addition, mirror neurones are thought to be involved in learning speech through imitation and are found in Broca's area.[239] If the rostral body enlargement is associated with mirror neurone dysfunction in the premotor area and these abnormalities extend to Broca's area this may also explain the observed association.

In contrary to hypothesis 3 a decrease in right prefrontal gyrification was seen. This disagrees with the previous study of GI in autism which reported a decrease in the left prefrontal lobe.[120] The difference in results may relate to methodological differences between the studies. The current report considers GI across the whole prefrontal lobe whereas the previous report examined one coronal slice just anterior to the corpus callosum. GI values may differ markedly between slices therefore a single slice estimate may not reflect the cortical folding pattern across the whole prefrontal lobe.

The right prefrontal hypogyrification in the autism group and the reduction in the area of the genu in both the PDD-NOS and autism groups are likely to relate to deficits in executive function which have been frequently reported in PDD.[27] The reduction in GI

seen in the autism group occurs in the absence of volume reductions, suggesting it is independent of cortical growth. In fact a non-significant increase in prefrontal volume was seen in the autism group therefore the low GI is likely to reflect aberrant prefrontal connectivity, consistent with the reduction in genu size. As discussed in section 4.2 van Essen proposed that closely connected cortical regions will be attracted closer together due to tension exerted along neuronal axons leading to those with fewer interconnections remaining spatially more dispersed. Thus, in autism it is possible that less local interconnectivity has led to less tension and hence less folding. However, one would expect a reduction in prefrontal white matter volume to accompany the reduction in GI if there were fewer axonal fibres running between regions. An alternative explanation is that there is a relative overconnectivity between regions which are usually poorly connected thereby producing abnormal axonal tension which opposes gyral development and hence leads to a reduction in cortical folding. Such overconnectivity is consistent with the idea that a larger less well organised brain may lead to the poor co-ordination of brain regions required to accomplish complex tasks such as language and social interaction.[167] Interestingly the PDD-NOS subjects did not show the GI reduction observed in autism and instead displayed a (non-significant) reduction in prefrontal volume. It is possible that such a volume reduction may also lead to autistic features but for the more severe phenotype to become manifest it is disordered, rather than reduced, connectivity which must occur.

There were no significant differences found between the groups with respect to the whole brain or prefrontal volumes. This disagrees with the findings of the meta-analysis

reported in Chapter 3 in which autistic individuals were found to have consistently enlarged brain volumes throughout life. Autism is a heterogenous disorder and it is possible that differences in the method used to identify autistic subjects between the current study and those in the meta-analysis may account for these differences. The current studied used the SCQ, a screening instrument based upon the ADI-R, to delineate the groups whereas the majority of studies included in the meta-analysis used much stricter diagnostic criteria for autism, usuallya combination of the ADI-R, ADOS and DSM criteria. The latter approach is clearly more likely to pick out truly autistic subjects but it has the drawback that it those identified may represent a subgroup of the autistic population with more severe symptoms than the generality of this population. It is possible that more severely affected autistic individuals show lifelong brain enlargement whereas those who are less severely affected do not.

7.3 Comorbidity of Pervasive Developmental Disorders and Schizotypy

Clinical Features

When the main PDD-NOS group is divided into those with and without schizotypal features it becomes apparent that the high rates of psychopathology in this group are in fact driven by the group which is comorbid for PDD-NOS and schizotypy. This comorbid PDD-NOS group have similar levels of psychotic phenomena to the SIS+ subjects and higher rates of other symptoms such as fatigue, irritability and depression They are markedly dissimilar to the non-comorbid PDD-NOS group who have low rates of morbid pathology on most of the measured symptom.

Neurostructural data

A similar pattern to the MRI findings is seen to the clinical findings described above. Again the comorbid PDD group appear to be broadly similar to the SIS+ group while those with PDD-NOS alone differ significantly from both. There are no significant differences between the autism and the comorbid autism groups with the right prefrontal GI being similarly reduced in both, albeit the main effect was non-significant for this measure. It is worth noting that the autism group did have non-significantly larger prefrontal lobes than the comorbid autism group and it is possible that this lack of significance relates to issues of power.

Both the clinical and the brain structural data are in keeping with the hypothesis that within the PDD group as a whole there is a sub-group of individuals who, although they

have features of PDD, bear more resemblance to schizotypal individuals than they do to those with PDD alone. In contrast the comorbid autism group are more similar to the autism group than to the SIS+ group which suggests that these individuals have schizotypal features as part of their autism as opposed to a primary diagnosis of schizotypy.

7.4 Limitations of the Study

There are a number of important limitations to the current study which require consideration. It is important to note that while the cut-offs on the SIS and the SCQ are empirically and independently derived, neither of these instruments are intended as diagnostic tools. Hence, each of the groups derived from these rating scales do not necessarily conform to actual diagnostic categories and thus may contain individuals with varying clinical pictures. However such heterogeneity is most likely to obscure differences between the groups meaning that from this perspective the results reported should be regarded as conservative. In addition, this risk of type II error is compounded in the final analysis by the small group sizes.

The population examined is a heterogeneous one and some subjects will have specific educational impairments over and above the schizotypal and autistic features that define the subject groups. Should one of these impairments be more greatly represented in one of the subject groups compared to others then it is possible that any differences found may be due to this and not to the feature which defines the groups. However, given the neurodevelopmental nature of schizotypy and of pervasive developmental disorders it is likely that any such increase in specific impairments would be related to the cognitive deficits known to be associated with the disorders themselves.

The issue of more general IQ impairments and their relationship with each of the groups is more thorny. In the current study an IQ matched control group was used in each of the

analyses as well as the normal control group. Disagreements exist about whether the use of an IQ matched control group is appropriate especially in the autism literature. There are many who argue that low IQ is part of the autistic syndrome and that to use an IQ matched control group will obscure differences which relate to the syndrome itself.[240] There are also difficulties in the selection of an appropriate IQ matched group – does one choose a defined syndrome such as Down syndrome or a idiopathic low IQ group which will be confounded by a number of factors such as obstetric complications and socioeconomic deprivation. The contrary argument is that by not taking into account IQ one risks false positive findings that are related to general cognitive impairment rather than to autistic features.[146] There is no definitive answer to this problem, however it seems prudent to use an IQ matched control group in addition to a healthy control group and in fact most of the differences found in the current study were present when the subject groups were compared to either group of controls.

Finally, no attempt was made to correct for multiple comparisons thus inflating the risk of a type I error particularly in the structure-symptom analysis which was post-hoc. It is worth noting that more significnant results were returned than one would expect through chance alone (i.e. more than 1 in 20 tests were significant) but many of the differences would not remain significant if a correction for multiple comparisons was applied. Those results which confirmed predetermined hypotheses are unlikely to have arisen by chance alone but caution is urged in the interpretation of results which were not predicted prior to undertaking the experiment, e.g. the reduction in GI seen in the autism group and the

structure-symptom relationships. These results are still valuable in guiding future research and allowing the development of new hypotheses to be tested.

7.5 Final Remarks and Directions for Future Research

At present all psychiatric diagnoses are based on the subjective assessment of expressed thoughts and observed behaviours and are thus imperfect categories with considerable overlap. In individuals with cognitive impairment the discrimination between diagnostic categories is further complicated by other factors such as low IQ and poor communication skills. The work presented in this thesis represents the first steps in determining the relationship between overlapping disorders in this population and in delineating the diagnostic boundaries between them. In Chapter 1 two possible relationships between schizotypy and ASD were proposed, i.e. they may represent part of the same spectrum of disorders or they may represent discrete disorders with overlapping phenotypic features. The data presented above support the latter hypothesis, with differences between PDD, autism and schizotypy being apparent both clinically and at the neurostructural level. In addition, it may be that within the broader population of individuals with PDD there is a group with features consistent with a diagnosis of PDD but who are in fact suffering from a schizophrenia spectrum disorder.

The future development of objective diagnostic methods to discriminate psychiatric disorder has clear benefits for the management and prognosis of affected individuals and thus for the provision of appropriate clinical services. Using the conditions considered in this thesis as an example, it is possible that schizotypal individuals may gain benefit from antipsychotic treatment whereas those with PDD alone may not. The use of

antipsychotics in PDD is becoming increasingly common and it may be that there are some people who are unnecessarily medicated and conversely some who are not. In addition, the selection of appropriate psychological treatment is hampered by an unclear diagnosis - clearly if an individual is socially withdrawn due to the presence of ideas of reference then they will require different treatment strategies to those who lack desire for social contact at all. The prognostic issues are of equal if not greater importance due to the possibility that in schizophrenia early treatment of high risk individuals may help to delay or even avert the onset of illness.[241]

The first step in developing the findings presented above is to carry out a more detailed parcellation of the frontal lobe and to examine the temporal lobe, abnormalities of which are implicated by the reduced size of the isthmus in the schizotypal group. This would elicit any differential enlargements or reductions in these lobes and provide further information as to exactly which parts of the brain are responsible for the phenotypic features of autism and schizotypy. As part of the ESC each of these individuals will receive a second MRI scan around 18-24 months after the first assessment. As it was in the EHRS, this is likely to be highly informative with regard to the evolution of psychiatric symptoms and may confirm the predictions of a reduction in prefrontal volume around or before the onset of schizophrenia.

In addition to the clinical and neuroimaging data there is a raft of other data collected on these individuals as part of the ESC. This includes neuropsychological measures of frontal lobe function and memory, and putative aetiological variables including genetic

data, early medical history and obstetric complications. Examination of the neuropsychological measures with respect to brain structure may shed light on the nature of the abnormalities observed on MRI, in particular whether they are deleterious or compensatory. This will be especially useful if changes in neuropsychological function over time are compared to brain structural changes over the same period. Although not part of the current data collection for the ESC, it is highly likely that functional MRI and diffusion tensor imaging would also provide further insights into the nature of brain structural changes. Finally the aetiological data should be examined with respect to brain structural and functional abnormalities. This approach is likely to provide insight into the development of disorder and hence possible targets for future intervention.

Moving beyond the ESC, further research is required to examine the nature of the overlap between autism and schizotypy. The findings presented above suggest that diagnostic confusion could lead to the misclassification of schizotypal individuals as suffering from PDD. However the groups were small and the SIS and SCQ ratings do not necessarily reflect true diagnostic categories therefore future studies should use large, well defined groups. Such studies may lead to the development of criteria that reliably separate the disorders which, given the implications of diagnostic uncertainty, would be invaluable.

Chapter 8

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